# Functional hemispheric asymmetries in emotional processing and nosognosia

Thesis

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***To Luca and Noemi

# Abstract

Aim of the present doctoral thesis was to investigate how the human brain builds a positively biased picture one's own health state. The first part of the section "own contributions" is dedicated to the study of positive illusions in the process of self-evaluation. The second part introduces two experiments on lateralized emotional processing, with a special focus on the influence of emotion on spatial attention.

*Anosognosia* designates the inability to recognize one's own illness. Representing one of the most striking and enigmatic forms of agnosia, no model is currently able to account fully and comprehensively for the phenomenon in its scope and complexity. Unlike previous investigations focusing on dysfunction, the present thesis emphasizes the study of the *normal function* impaired in anosognosia, a function reasonably labeled *nosognosia*. Nosognosia is the function that continuously monitors our own well-being, against the background of interoceptive and external changes. It comprises not only the detection of signs of illness, but also the ability to realistically estimate one's future health state. Many studies showed that the latter is generally biased towards optimism and that healthy people display a strong tendency to view themselves as less likely than others to turn ill. This positive illusion is called *unrealistic optimism*.

We argue that there is a qualitative similarity between clinical confabulatory behavior and unrealistic optimism. Conceptualizing the optimistic attitude inherent to nosognosia as a form of "prospective anosognosia", *study 1* supports this view. In the same way it abolishes anosognosic denial, left-ear cold water irrigation reduced unrealistic optimism for one's own future health state in healthy subjects. This finding indicates the right parieto-insular cortex – activated by this procedure - as a key structure for the appraisal of one's own vulnerability to illness.

*Study 2 and 3* investigate brain lateralization of emotions, exploring the interaction between emotional processing and spatial attention. We found a modulation of spatial attention by emotional states and traits with a strong association between negative affect and leftward hemispatial attention. Our results validate the predominant role of the right hemisphere in negative emotions and indicate the importance of the parietal lobes in the processing of non-spatial contents.

Together, the findings of the experiments with healthy volunteers are consistent with clinical observations from patients with unilateral brain lesions as well as with previous findings collected in healthy populations. They corroborate the existence of functional hemispheric asymmetries in both self-awareness and emotional processing and support the view of a right hemisphere specialization for both the ability to recognize one's own illness and to process negative emotions.

# Zusammenfassung

Ziel der vorliegenden Dissertation war zu untersuchen, wie das menschliche Gehirn ein Bild des eigenen Gesundheitszustandes aufbaut, das systematisch zur emotional positiven Seite hin verzerrt ist.

Der erste Teil betrifft das Studium der positiven Illusionen, welche die Selbsteinschätzung begleiten. Der zweite Teil konzentriert sich auf die hemisphärische Lateralisierung der emotionalen Verarbeitung, mit speziellem Fokus auf den Einfluss der Emotionsvalenz auf die räumliche Aufmerksamkeit.

*Anosognosie* bezeichnet die Unfähigkeit, die eigene Krankheit zu erkennen. Sie stellt eine der eindrucksvollsten und rätselhaftesten Formen von Agnosie dar. Keines der existierenden Modelle kann den vollen Umfang der klinischen Manifestationen dieses Phänomens erklären. Im Gegensatz zu bisherigen Untersuchungen, die den Schwerpunkt auf die Dysfunktion legen, betont die gegenwärtige Dissertation das Studium der *normalen Funktion*, die in der Anosognosie beeinträchtigt ist; eine Funktion, die hier naheliegenderweise als *Nosognosie* bezeichnet wird.

Nosognosie ist die Funktion, die vor dem Hintergrund von interozeptiven und externen Veränderungen das eigene Wohlbefinden überprüft. Sie erfasst nicht nur die Wahrnehmung allfälliger Krankheitszeichen, sondern auch die Fähigkeit, das eigene Krankheitsrisiko realistisch einzuschätzen. Eine Fülle von Studien zeigen, dass diese Einschätzung systematisch verzerrt ist und zwar zur positiven Seite hin. Insbesondere weisen Gesunde eine starke Tendenz auf, das eigene Risiko für zukünftige Erkrankung als deutlich geringer zu erachten im Vergleich zum Risiko der Mitmenschen. Die Unterschätzung der eigenen Vulnerabilität für Krankheit wird als *unrealistischer Optimismus* bezeichnet.

Wir denken, dass es eine konzeptuelle Ähnlichkeit zwischen dem klinischen konfabulativen Verhalten und dem unrealistischen Optimismus gibt. Wir haben deshalb die optimistische Fehleinschätzung als „prospektive Anosognosie“ aufgefasst. Die *Studie 1* bestätigt unsere Hypothese, dass ähnliche neuropsychologische Prozesse der Anosognosie und dem gesunden unrealistischen Optimismus zu Grunde liegen. So wie sie die Anosognosie bei Patienten aufhebt, führte die kalorische Stimulation des linken Ohrs mit kaltem Wasser zu einer

Reduktion des unrealistischen Optimismus in gesunden Probanden. Dieser Befund deutet darauf hin, dass der rechte parieto-insuläre Kortex – aktiviert bei dieser Methode - eine für die Einschätzung der eigenen Vulnerabilität für Krankheit wichtige Struktur ist. Die *Studien 2 und 3* untersuchten die Hirnlateralisierung der Emotionen und die Interaktion zwischen emotionaler Verarbeitung und räumlicher Aufmerksamkeit. Wir beobachteten eine Assoziation zwischen persönlichkeitseigener Tendenz zur Bevorzugung der linken Raumhälfte („Pseudoneglekt“) und dem Verarbeiten spezifisch negativer Emotionen (Studie 2) und eine Modulation der räumlichen Aufmerksamkeit durch die momentane Befindlichkeit (Studie 3). In ihrer Gesamtheit stützen die Resultate vorliegender Dissertation die dominierende Rolle der rechten Hemisphäre in der Verarbeitung negativer Emotionen und heben die Bedeutung der Parietallappen und ihrer Verbindungen für die Verarbeitung nicht-räumlicher Inhalte hervor.

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"Even if all our senses are intact and our brain functioning normally, we do not have direct access to the physical world. It may feel as if we have direct access, but this is an illusion created by our brain"

Chris Frith

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# Abbreviations

| | |
|---|---|
| rACC | Rostral anterior cingulated cortex |
| AHP | Anosognosia for hemiplegia |
| AIC | Anterior insular cortex |
| BAS | Behavioral activation system |
| BIS | Behavioral inhibition system |
| CI | Caloric irrigation |
| CVS | Caloric vestibular stimulation |
| EEG | Electroencephalography |
| fMRI | Functional magnetic resonance imaging |
| LH | Left hemisphere |
| LVF | Left visual field |
| MEG | Magnetoencephalography |
| PET | Positron emission tomography |
| RH | Right hemisphere |
| RVF | Right visual field |
| TMS | Transcranial magnetic stimulation |
| UO | Unrealistic optimism |

# 1

# General Overview

## 1.1 Anosognosia: the denial of illness

### 1.1.1 Overview

The term *anosognosia* originates from Greek *a* = without; *nosos* = disease and *gnosis* = knowledge. It refers to a neurological condition (first described in 1885 by Von Monakov) belonging to the disorders of "loss of knowledge", grouped under the term of agnosias. The term anosognosia was introduced in the early 20$^{th}$ century by Joseph Babinski (1857-1932), a French neurologist, student of Charcot and contemporary of Freud, to describe the impressive condition in which patients paralyzed on one side of their body claim that they are in fact perfectly able to move (Babinski, 1914). Originally intended to designate unawareness of hemiplegia, the term anosognosia has recently reached a broader meaning. Nowadays, most writers would agree that "anosognosia" quite generally designates the inability to recognize one's own illness or disability. Nevertheless, it is recognized as a heterogeneous neurological disorder, which may selectively impair awareness of any sensory, perceptual, motor or cognitive deficits.

Many forms of anosognosia have been described (They are summarized in Table 1). Some examples of altered self-awareness comprise cortically blind patients, who claim that they can see (so-called "*Anton syndrome*"; Anton, 1896; Goldenberg et al., 1995), aphasic patients who are unaware of their language deficits (Shuren et al., 1995), Alzheimer's patients who fail to acknowledge their memory impairment (Kristin & Robin, 2007; Starkstein et al., 2006), as well as patients suffering from *hemispatial neglect* (i.e. failure to explore the side of space contralateral to the lesion) being convinced to equally explore both sides of space (Buxbaum et al., 2004). In all forms of anosognosia, unawareness can vary in severity, reaching from a simple indifference toward one's own illness or deficit – a condition designated with the term of *anosodiaphoria* (Babinski, 1914) - an active and vehement denial of one's own disability accompanied by confabulations (Marcel et al., 2004). Anosognosic symptoms may fluctuate and in case of anosognosia for hemiplegia (AHP) they usually become less intense over time. They occur more frequently and are more severe after right hemisphere (RH) lesions, and their incidence is higher after large lesions, comprising cortical and subcortical brain areas (Pia et al., 2004). In the last two decades, many authors investigated the anatomical correlate of denial (especially related to hemiplegia), trying to identify which regions are specifically damaged when anosognosia is observed. While most studies agree that lesions usually involve the RH, the intra-hemispheric localization of the damage leading to anosognosia appears more controversial. In fact, it seems that a unique and circumscribed "awareness area" causing, when damaged, denial, does not exist. Awareness probably relies on the integrity of a network that involves different cortical and subcortical brain regions (recent anatomical findings concerning specifically AHP will be considered in the next chapter). Since a failure in illness recognition has serious consequences for recovery and may impair the efficacy of rehabilitative measures, the study of anosognosia is not only of theoretical interest but also of great clinical relevance. That is why anosognosia has aroused broad interest among scientists and clinicians alike.

The majority of neuroscientists focused on AHP trying to clarify the neural basis of motor awareness (Marcel et al., 2004). The large interest for AHP should not surprise if one considers the impressive character of this particular type of denial and the ways it affects recovery of motor functionality and interferes with motor rehabilitation. In the next chapter, anatomical correlates, diagnostic tools and major pathogenetic models for AHP will be reviewed in detail.

Anosognosia is commonly diagnosed with the help of questionnaires (Bisiach et al., 1986), which allow to characterize the disorder and to assess the severity of unawareness, by asking the patient a series of targeted questions. When approaching anosognosic symptoms, three main aspects need to be considered in order to characterize the lack of awareness. These aspects are *extension, specificity* and *partiality* (Marcel et al., 2004). *Extension* refers to what kind of awareness is compromised. Awareness of deficit is not a unitary phenomenon and includes different levels, which may be independently compromised. For example, a patient may be aware of his deficit but fail to recognize the functional consequences linked to the deficit. The ability to realistically predict the outcome of own performance is an important and measurable facet of awareness, which has to be considered in each anosognosic patient (Fischer et al., 2004). *Specificity* means the degree to which lack of awareness is restricted to a particular deficit. A patient suffering from hemiplegia may fail to acknowledge the paralysis of his arm while (at the same time) recognising the motor deficit in his leg. An extraordinary example of specificity of anosognosia is reported by Ramachandran (1995), who describes a patient with AHP who refuses a box of candy saying "I am diabetic, doctor-I can't eat candy. You should know that!" (Ramachandran, 1995, p. 25). In other words, this patient denies her paralysis while acknowledging her diabetes and the implications of this illness.

The concept of *partiality* implies that unawareness of one's deficit may be less than total and suggest that some implicit knowledge about the deficit may be present, even in severe form of anosognosia. Patients who deny illness but are willing to stay in hospital are not rare, which indicates that a kind of implicit awareness might be present. In their study, Nardone and colleagues presented a series of words, some of them associated with hemiplegia-related deficit, to a group of anosognosic patients and to a control group. They found that, in contrast to non-anosognosic patients, patients who deny the own hemiplegia take longer to respond to words concerning paralysis (like “handicapped”), body part (like “arm”) or mobility (like “athletic”), finding support for the notion of an implicit knowledge. Increased latencies presumably result from the attempt of maintaining deficit-related thoughts outside from consciousness, a defence mechanism called “repression” by psychoanalytic psychologists (Nardone et al., 2007).

The remarkable improvement of neuroimaging techniques allowed important advances in the understanding of this heterogeneous condition. However, none of the existing models offers an exhaustive explanation of anosognosia. The neural mechanism accounting for illness awareness – impaired in different forms of anosognosia – has to date not been identified and many questions remain unanswered. It is likely that each form of anosognosia involve a distinct pathogenesis, through this does not exclude some neural circuits common to all types of denial.

**Table 1: Forms of anosognosia**

| ***Authors, year*** | ***Major form of anosognosia*** | ***Description*** |
|---|---|---|
| Babinski, 1914 | Anosognosia for hemiplegia | Unawareness of hemiplegia<br>Patient denies his paralysis, is unable to recognize his inability to move |
| Anton, 1896 | Anosognosia for cortical blindness "Anton syndrome" | Lack of awareness of being blind<br>Cortically blind patient affirms that he is able to see |
| Buxbaum et al., 2004 | Anosognosia for neglect | Lack of awareness of hemi spatial attentional deficit. Patient believe to equally explore both sides of space |
| Starkstein et al., 2006; Kristin and Robin, 2007 | Anosognosia for memory impairment in Alzheimer's disease | Patient fails to recognise his memory deficits and is unable to realistically judge his cognitive performance |
| Shuren et al., 1995 | Anosognosia for aphasia | Unawareness of language impairment. Patient fails to acknowledge his speech errors |
| Babinski, 1914 | Anosodiaphoria | Milder form of anosognosia. Patients verbally acknowledges his deficit but shows lack of interest to it |
| Critchley, 1962 | Misoplegia | Patient express hatred toward the affected limb, often accompanied by verbal or physical abuse |

### 1.1.2 Anosognosia for hemiplegia (AHP)

Anosognosia for motor impairment in stroke patients is one of the most fascinating phenomena in clinical neurology. Patients suffering from AHP are convinced that their paretic or plegic limb functions normally; they overestimate their motor ability and sometimes produce implausible explanations, when confronted with an obvious failure to execute a required action. The lack of awareness of hemiplegia following an acute brain lesion is a temporary condition generally lasting from a few hours to a few days, although some rare cases of chronic anosognosia, lasting several weeks, are described in the literature (Cocchini et al., 2002). The main reason why AHP is the most studied form of anosognosia may be the ineffectiveness of rehabilitation during its presence. AHP is a complex and multifaceted phenomenon, which can manifest itself in many different ways. As noted above, it can be quite specific: patients generally do not fail to recognize other disabilities, they do not overestimate other motor or cognitive own abilities. AHP may also selectively concern only one limb: arm plegia can be denied whereas leg paralysis acknowledged. Awareness is not a unitary phenomenon and, when assessing AHP, it is important to consider that lack of awareness of paralysis may dissociate from unawareness of its consequences, or from the inability to realistically estimate the outcome of one's own motor performance (Marcel et al., 2004). In some cases, AHP might be accompanied by altered limb perception, leading to somatoparaphrenia (i.e. lack of ownership of a paralysed limb) or misoplegia (i.e. morbid dislike or hatred of paralysed limbs in patients with hemiplegia) (Critchley, 1962; Vallar & Ronchi, 2009 for an overview).

*Incidence*

In recent times, many researchers tried to determine the incidence of AHP in stroke patients. Probably as consequence of the different criteria used to diagnose anosognosia as well as differences in the time elapsed since stroke, these studies produced a wide variation of results (Orfei et al., 2007). Some investigators considered a patient's failure to spontaneously report the motor deficit a sign significant enough to diagnose AHP. Others have insisted that an extensive questioning about paresis or plegia would be indispensable for the diagnosis. Recently, a study conducted by Baier and Karnath (2005) on a sample of 128 patients indicates that, if a conservative cut-off criterion is applied for the diagnosis (i.e. direct questioning necessary), the incidence of AHP ranges from 10% to 18%. AHP can be classified as mild, medium or severe. Anosognosic denial is much more frequently observed following RH lesions. The study of Breier et al. (1995) was based on observations of anosognosia after intracarotid barbiturate injection. It showed that of the 37 patients, 89% exhibited anosognosia for hemiparesis after right-sided injection whereas only 49% after left-sided injection showed similar symptoms. Not surprisingly, anosognosia is equally frequent in male and female and no age-related difference has been evidenced (Pia et al., 2004).

*Anatomy*

Anosognosia is most frequently of a vascular aetiology. Typically, frontal, parietal or temporal cortical regions are damaged, but the disorder may also emerge in conjunction with subcortical lesions, most often affecting the basal ganglia and the thalamus (Pia et al., 2004). Berti and colleagues found that AHP is often associated with premotor and somatosensory cortex lesions, areas related to motor planning and execution (Berti et al., 2005).

Other recent neuroimaging studies indicated the insular cortex as an important anatomical structure related to AHP. They show that this region is involved in self-awareness, including movement awareness: the insular cortex is supposed to integrate input signals related to self-awareness about the functioning of body parts (Karnath et al., 2005). More specifically, the anterior insular cortex (AIC) seems to play a key-role in different aspects of self-awareness (Craig, 2009). Its integrity is essential; it underlies the human capacity to be aware of the own person, and damage affecting this region – which some authors consider to represent the neural correlate of consciousness - may disrupt awareness and lead to anosognosic denial.

As previously mentioned, AHP is more often reported after right than after left hemisphere lesions (LH) (Pia et al., 2004). This clinical evidence has some implications for the lateralization of higher cognitive functions. Although some authors contend that the frequency of anosognosia in left brain damaged patients may have been underestimated due to aphasic symptoms often accompanying LH lesions (Cocchini et al., 2009), the majority agree that the RH is primarily dominant for an individual's awareness of one's own corporeal being and its relation to the environment and affective state (Devinsky, 2000). Several lines of evidence suggest that the RH plays a crucial role in the monitoring of one's own physical, emotional and social self. Indeed, it is known that its injury may impair a series of functions related to self-awareness, among others the ability to recognize own illness. RH lesions cause also left-sided neglect, disordered ego boundaries, reduplicative delusions, topographic disorientation and various disorders of socially relevant behavior.

Furthermore, adding support for the notion that self-awareness is a right lateralized function, some researchers found that RH inactivation with intracarotid amytal injection (Wada test) lead to higher prevalence of denial than LH inactivation. This finding strongly suggests that the monitoring of the source of agency over motor performance is predominantly a RH function (Adair et al., 1995; Gilmore et al., 1992).

*Diagnosis*

As anticipated above, when diagnosing AHP, three crucial aspects should be considered: the degree to which lack of awareness is restricted to a particular deficit (*specificity*), what kind of awareness is compromised (*extension*) and whether some implicit knowledge about the deficit is spared (*partiality*) (Marcel et al., 2004).

The diagnosis of AHP is typically based, besides a clinical observation of the patient, on questionnaires (Bisiach et al., 1986; Feinberg et al., 2000). Both methods have the aim to measure the severity of the disorder and to describe anosognosia in terms of specificity, extension and partiality. Tables 2 and 3 show two frequently used scales to grade the severity of anosognosia in different ways.

**Table 2: Bisiach's Scale for the assessment of AHP (Bisiach et al., 1986)**

| |
|---|
| Grade 0 (no anosognosia): the disorder is spontaneously reported or mentioned by the patient following a general question about their complaints |
| Grade 1: the disorder is repoted only following a specific question about the strength of the patient's limbs |
| Grade 2: the disorder is acknowledged only after demonstrations through routine techniques of neurological examination |
| Grade 3: no acknowledgement of the disorder can be obtained |

**Table 3: Anosognosia for hemiplegia questionnaire (Feinberg, 2000)**

1. "Do you have weakness anywhere?"
2. "Is your arm causing you any problems?"
3. "Does it feel normal?"
4. "Can you use it as well as you used to?"
5. "Are you fearful about losing your ability to use your arm?"
6. "Is the sensation in your arm normal?"
7. "The doctors tell me that there is some paralysis of your arm. Do you agree?"
8. (Left arm is lifted and dropped in left hemispace.) "It seems there is some weakness. Do you agree?"
9. (Left arm is lifted and dropped in right hemispace.) "It seems there is some weakness. Do you agree?"
10. "Take your right arm, and use it to lift your left arm. Is there any weakness of your left arm?"

Responses for each item were scored as 0 if the patient showed awareness of deficit; 0.5 for partial awareness; and 1.0 for complete unawareness or denial. The scores were summed to produce a total score on the scale ranging from 0 (no anosognosia) to 10 (maximum anosognosia).

Additionally, questions on bimanual tasks abilities are helpful for assessing awareness of the consequences of hemiplegia and allow to cover all facets of awareness (Nimmo-Smith et al., 2005). Fig. 1 (part A) shows a series of questions that can be use to quantify patient's unawareness of inability to perform tasks requiring bilateral use of limbs. Typically, patients exhibiting severe anosognosia are not aware of the activity limitations of the affected limb, so when asked to predict own performance they overestimate own motor abilities.

A comprehensive bedside examination should thus include both conventional generic questions ("what is wrong with you?", "Is your arm causing you any problems?") and questions involving imagined abilities (ideally one bimanual "how well could you in your present state tie a knot?" and one bipedal "how well could you jump?"). Generic questions and questions relating to imagined actions reflect different levels of unawareness of motor incapacity. Only if both are addressed will the examiner get information about the true extension of unawareness.

Intriguing, evidence suggests that some patients show a dissociation within awareness, according to the viewpoint (1st or 3rd person) of the question (Marcel et al., 2004). The same patient may overestimate his abilities when asked how well he could perform a task in his current state (1st person perspective); whereas no overestimation is reported, if the same question is asked from a 3rd person perspective (i.e. "If I (experimenter) were in your present state, how well would I be able to jump, compared with my usual ability?"). This fact calls into question the role of motivation and self-protective mechanisms.

Unfortunatly, the existing methods rely heavily on language, which may represent a problem when testing aphasic patients. To counter this problem, Della Sala and colleagues (2009) proposed a new tool, the VATAm (Visual-Analogue Test for Anosognosia for motor impairment). This test, which includes a 4-point visual-analogue scale, is less dependent on language and overcomes limitations of previous assessment methods (see Fig. 1, part B).

''In your present state how well, compared with your normal ability, can you…

***Bimanual tasks***

…tie a knot?

…clap your hands?

…shuffle cards?

…row a boat?

…unscrew bottle?

***Bipedal task***

…climb a ladder?

…jump?

If you can do it as well as usual, say 'ten'',
''If you cannot do it at all, say 'nought'.''
*An estimate of 5 or more is counted as overestimation on that question.*

**Figure 1a: Bilateral tasks questions for assessing awareness of the consequences of hemiplegia (Nimmo-Smith et al., 2005)**

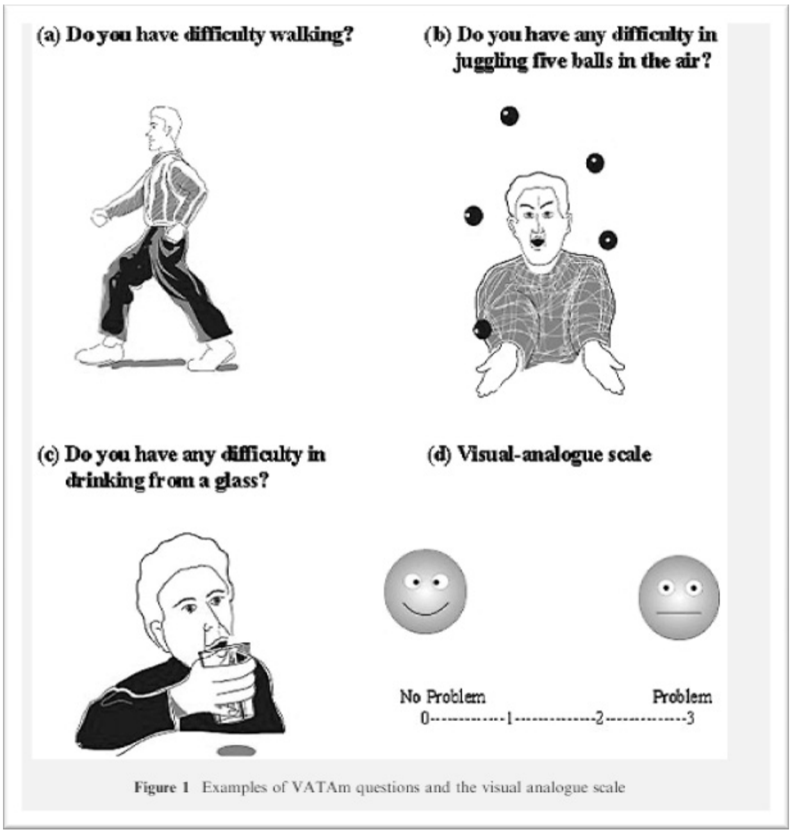


Figure 1 Examples of VATAm questions and the visual analogue scale

**Figure 1b: Visual-Analogue Test for Anosognosia for motor impairment (VATAm), Della Sala et al. (2009)**

Patient and two caregivers designate a score from 0 (no problem) to 3 (problem) to each question.
A total score VATAm score is calculate by adding the scores from the 12 questions.
The patient's total rating is subtracted from that of their caregivers.
The caregiver-patient discrepancy ranges from -36 to +36 and indicates the degree of anosognosia. Positive values indicate that the patient overestimates his motor abilities (i.e. anosognosia), a negative ones that he underestimates his motor abilities.

Below a typical examiner-patient conversation, illustrating a case of severe anosognosia (Berti et al., 2007, pp. 173-174).

E: Where are we?

P: In the Hospital

E: Which hospital?

P: Somma Lombardo.

E: Why are you in the hospital?

P: Because I had a stroke.

E: What is a stroke?

P: I do not know.

E: How is your left arm?

P: Fine.

E: Can you move it?

P: Yes.

E: Would you be able to raise your left arm up in the air?

P: Yes, I would.

E: Would you be able to lift the telephone receiver with your left hand?

P: Yes, I would.

E: Would you be able to open a bottle, using both your hands?

P: Yes, I would.

E: Would you be able to brush your hair handling the hairbrush with your left hand?

P: Yes, I would.

E: Would you be able to wash your face using both your hands?

P: Yes, I would. (The patient was then asked to actually perform some movements.)

E: Could you touch my hand with your right hand?

P: (The patient does it without any problem.)

E: Could you touch my hand with your left hand?

P: (Although she seems to try the movements, she cannot raise the arm and reach the examiner's hand. Nonetheless, after a while she says 'Done.')

E: Have you done it?

P: Yes, I think so.

E: Could you touch your left hand with your right hand?

P: (She does it without problem, thus showing that the left personal neglect has vanished.)

E: Could you open this bottle for me, please?

P: (The patient attempts to do it using only the right hand.)

E: Can you manage?

P: No.

E: Why?

P: Because it does not open.

E: How do you open a bottle?

P: With one hand I hold the bottle, with the other I unscrew the cap.

E: Are you doing it?

P:Yes.

E: Can you put your left hand on your left shoulder?

P: Yes, I can.

E: Then please do it.

P: (the patient seems to try the movement: she also overtly looks at the left motionless

arm and at the shoulder. After that, she looks at the examiner, as if she had finished performing the requested action).

E: Have you done it?

P: Yes, I think so. (The patient, on the wheelchair, is taken to the bathroom and placed in front of the basin.)

E: Could you wash your face using both hands, please?

P: (The patient takes the bottle of the liquid soap with the right hand and attempts to soap her left hand as if the left hand was actually over the basin, near the midline. However, the left hand was not there because it was lying on her lap. After having soaped the ‘ghostly’ hand, she started to move the right arm/hand forward and backward as if she was washing the two hands, one against the other. Finally, she washed the face using the right hand.)

E: Are you washing both your hands?

P: Yes, I am.
E: Are you washing your face?
P: Yes, I am.
E: With both hands?
P: Yes, I think so. (Then the patient was asked to brush her hair handling the hairbrush with the left
hand. The hairbrush was on the table and the left hand was lying motionless on the table as well. She took the hairbrush with the right hand and forced it below the left hand. While 'holding' the hairbrush with the left hand she moved the head as if she was actually brushing the hair. After a while, she looked at the examiner and seemed satisfied with her performance.)
E: Have you done it?
P: Yes, I have, but only on the left side.

*Theories of anosognosia*

Theoretical accounts of AHP continue to be the subject of controversies. Over the past fifty years, many models have been proposed to explain the disorder. However, to date, none of them is able to account fully and exhaustively for the phenomenon in its complexity and many issues still remain unresolved. Some of the most important theories are briefly reviewed here (Orfei et al., 2007).

Early investigators focused on the role of motivation, assuming that AHP would result from a defence mechanism, preventing depressive feelings (Weinstein & Kahn, 1955). Alternatively, other authors considered AHP to be caused by a proprioceptive loss and a general cognitive impairment ("*discovery theory*", Levine et al., 1991). The *discovery theory* proposes that anosognostic patients are not able to recognize their paralysis because the sensory feedback that normally informs an individual about the position and movement of limbs is damaged.
To date, the validity of these two theories (motivational and discovery theory) is questionned. The scientific community currently agrees that neither psychological

defense nor sensory and intellectual loss, are fully responsible for the genesis of anosognosia. Nonetheless, some authors admit that self-protective mechanisms and emotional reactions to functional loss may play some role for the emergence of the disorder (Turnbull et al., 2005).

In 1965 Geschwind formulated the *Interhemispheric disconnection hypothesis*, hypothesizing that confabulations exhibited by anosognostic patients may result from a functional split between the hemispheres. This disconnection would prevent information collected by the RH (controlling the left side of the body and indeed recognizing the paralysis at some nonverbal level) from being transferred to the speech-dominant LH (Geschwind, 1965).

The frequent association of neglect and anosognosia for motor loss following RH damage made some researchers conceive AHP as a secondary consequence of spatial or personal neglect (Cutting, 1978). However, later investigations demonstrated that AHP and neglect may dissociate, showing that AHP cannot be ascribed to the hemi-attention syndrom (Bisiach et al., 1986).

Still other authors suggested that AHP results from a failure to transfer new information from working memory into long-term memory. Patients suffering from AHP would fail to integrate observed motor impairments into their body self-image in long-term memory (Marcel et al., 2004; Starkstein et al., 1992). One has to emphasize, however, the clinical evidence that some patients with AHP display intact memory performance. If anything, the disorder seems to reflect a *specific* mnestic deficit rather than a global memory impairment.

Ramachandran hypothesized that AHP results from a functional interhemispheric imbalance. He speculated that the LH seeks to maintain the continuity of beliefs, tends to deny discrepancies, and uses confabulation, while the RH, in contrast, plays the role of a "devil's advocate" and detects discrepancies (Ramachandran, 1994,

1995). After a RH lesion, the LH is supposed to be unsupervised, and anosognosia may be the consequence.
Another line of reasoning proposes that AHP may be the result of an abnormal affect regulation (Davidson & Irwin, 1999; Turnbull et al., 2005). It is hypothesized that a disruption in the generation of negative emotions, lateralized to the right (frontal) hemisphere, is responsible for unawareness of motor impairment.

Several models focused on processes involved in motor planning and motor control. Among the pioneers of this approach, Heilman (1991) postulated the *feed-forward model*, which represents one of the most advanced models, later modified and improved by other researchers. This model assumes that the motor deficit of a limb is recognized when the brain detects a mismatch between an intended movement and the actual motor performance. A module comparing intended and observed movements notices discrepancies. Patients with AHP are unable to generate movement intention, therefore no mismatch is generated in the comparator module and the patient does not recognize his/her paresis. The core of this theory is that in AHP the inability to generate motor intention leads to a failure of expectation, which prevent the patient discovering that no movement has occurred.
Berti and Pia (2006) proposed a modification of the Heilman's (1991) hypothesis, assuming that in AHP the comparator module itself is deficient. Frith (2000) further posited that awareness of initiating a movement is based on a representation of the predicted consequences of making that movement. Patients with AHP think that they can move, because the representations of both desired and predicted positions of the limb - responsible for the experience of movement - are intact (Frith et al., 2000).

More recently, Fotopoulou and colleagues (2008) offered experimental evidence that altered awareness of action exhibited in AHP is caused by a dominance (and not by a loss, as previously hypothesized) of motor intention over sensory feedback. In their experiment, they manipulated motor intention and visual feedback of a movement (using a prosthetic rubber hand) in patients with AHP and in hemiplegic patients without anosognosia. This was done in order to assess whether the intention to move one's left hemiplegic hand influenced the perception of movement of that hand. The authors found that motor intention has a selective effect in the AHP group. Indeed, when patients with AHP were instructed to raise their left arm, thus having the intention to move (a "self-generated" condition), they were more likely than patients without AHP to falsely detect movement of a motionless rubber hand and to claim they had moved it (disregarding visual information). This model postulates that AHP derives from a dominance of motor intention over any sensory feedback that would indicate a failure of movement.

Models explaining anosognosia by altered intentionality or by the disruption of sensory-motor mechanisms recently received the largest agreement within the scientific community studying AHP. However, an abnormality in motor planning cannot explain all the features of AHP and certainly cannot account for anosognosia accompanying non-motor deficits.
In particular, these models do not take into account the role of emotion and the relevance of a functional interhemispheric balance in generating motor awareness and in preventing confabulatory behavior, often exhibited in AHP (Ramachandran, 1995; Turnbull et al., 2005).

The most fascinating question emerging from the study of anosognosia is how the brain constructs a truthful image of one's self and how he succeeds to constantly revised it, integrating health and illness. This disorder reminds us that self-awareness is a highly malleable concept, resulting from a construction performed daily by the human brain.

There are currently no long-term treatments for anosognosia. As mentioned above, AHP is a temporary condition generally lasting from a few hours to a few days. In the majority of cases, anosognosia simply disappears over time. To date, only two experimental procedures has been shown to temporarily attenuated AHP: caloric vestibular stimulation (CVS) (Cappa et al., 1987) and, more recently, self-observation 'from the outside' (from a 3rd person perspective) (Fotopoulou et al., 2009).

*Caloric vestibular stimulation (CVS)*

CVS is a non-invasive technique traditionally used to test functionality of the vestibular system (Barany, 1906). The patient is oriented in a supine position with the head inclined 30° from the horizontal and cold or warm water (+/- 7 degrees Celsius from body temperature) is irrigated into the external auditory canal first of one, then of the other ear (Fitzgerald & Hallpike, 1942). This procedure creates a temperature gradient across the semicircular canals, altering the density of the endolymphatic fluid contained in the labyrinth. This mimics the endolymph movement normally induced by head turning and gives the subject the illusion of movement (see Figure 2). Two important parameters indicate the functionality of the vestibular system: the presence of nystagmus (i.e. quick horizontal involuntary, rhythmic eye movements) and subjective dizziness and nausea. Nystagmus usually appears after 10-20 sec after irrigation starts, and eye movements are recorded using an infrared camera. The absence of nystagmus indicates vestibular weakness.

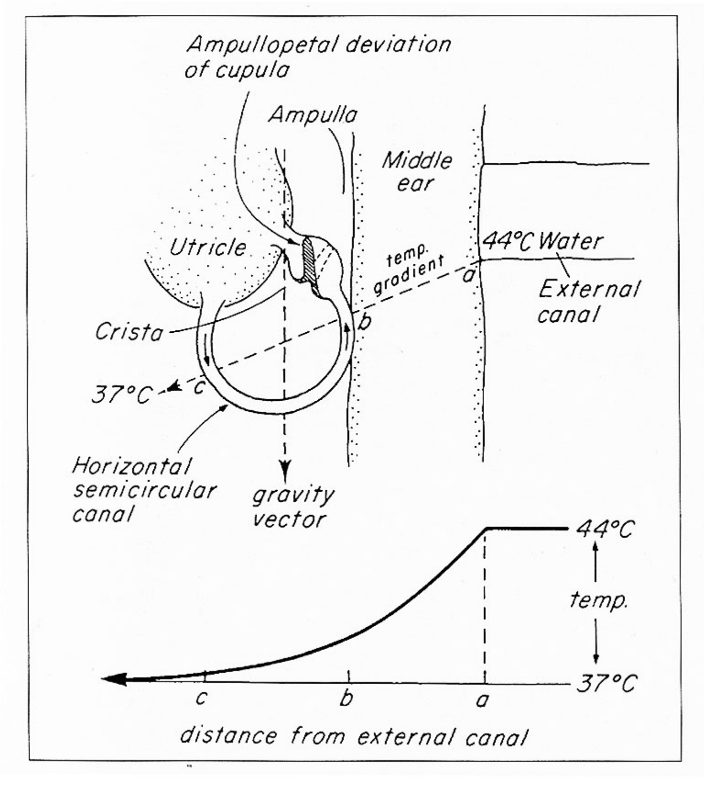


**Figure 2: Principle of CVS**
Irrigating cold or warm water (+/- 7° from body temperature) creates a temperature gradient across the semicircular canals, altering the density of the endolymphatic fluid and giving the illusion of movement.

Recent neuroimaging findings indicated that CVS activates primarily the parieto-insular cortex, which is considered the 'core region' of the multisensory vestibular cortex (Guldin & Grüsser, 1998). Cold-water irrigation activates predominantly brain regions contralateral to the stimulated ear, whereas warm-water rather activates the ipsilateral hemisphere. Furthermore, a recent PET study indicated that there is a dominance for vestibular cortical function in the non-dominant hemisphere (for right-handers the RH) (Dieterich et al., 2003). Figure 3 depicts this situation.

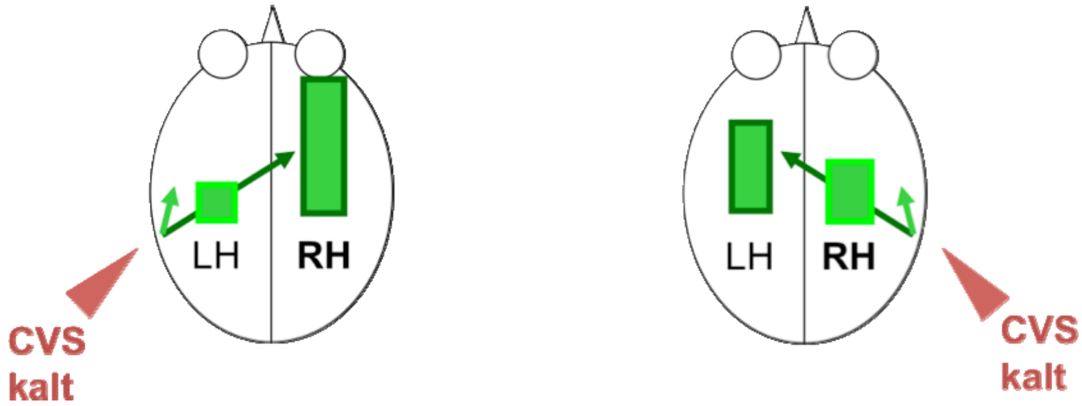


**Figure 3: Relative strength of heminspheric activation induced by cold-water CVS in a typical right-hander**

Beyond classical neurological investigations, this technique has been more recently exploited as a tool in the cognitive neurosciences, to explore hemispheric lateralization of cognitive functions in healthy individuals. For instance, Bächtold et al. (2001) investigated the effects of unilateral cold-water vestibular stimulation on spatial and verbal memory performance. Applying CVS during the encoding phase, they found better spatial-recall in participants stimulated in the left ear, and better verbal-recall in those stimulated in the right ear, as a result from temporary activation of cerebral structures contralateral to the stimulated ear. Other experiments evidenced that CVS modulates the phenomenon of binocular rivalry (BR) with ambiguous figures, demonstrating that this method activates neural mechanisms underlying perception (Miller et al., 2000).

Several studies demonstrated that ear irrigation with cold or warm water has an effect on a range of clinical conditions, among those neglect, anosognosia, somatoparaphrenia, mood disorder and phantom limb perception (Miller & Ngo, 2007).

Using warm- and iced-water CVS, Cappa et al. (1987) induced a temporary remission of anosognosia in two out of four patients suffering from AHP. Fifteen minutes after the stimulation, a previously completely anosognosic patient appeared to recognize his own motor impairment, affirming „I don't know why, I have always been able to move them, but now they are blocked: it is as if my brain is no longer able to command them" (Cappa et al., 1987, p. 780). Similarly, CVS induced temporary remission of somatoparaphrenic delusions in a patient convinced that her arm belonged to her mother (Bisiach et al., 1991). In both cases (anosognosia and somatoparaphrenia) the reported reduction of delusion was temporary and lasted just a few hours.

*Self-observation 'from the outside'*

More recently, Fotopoulou et al. (2009) reported the case of a patient with severe AHP, who recovered instantly and permanently when viewing herself in a video replay. In this patient, anosognosia did not reappear, and the video-exposure therefore revealed itself as therapeutic. As soon as the video stopped, the patient spontaneously commented: "I have not been very realistic". Examiner (E): "What do you mean?" Patient (P): "I have not been realistic about my left-side not being able to move at all". E: What do you think now?" P: "I cannot move at all". E: "What made you change your mind?" P: "The video. I did not realize I looked like this" (Fotopoulou et al., 2009, p. 1258) The authors argued that self-observation in videos and mirrors may bring about profound alterations in self awareness and that off-line self-observation may be spared in some patients.

## 1.2 Unrealistic optimism (UO)

*Optimism and positive illusions*

The word "optimism" derived from the Latin *optimus*, superlative of bonus (= good), meaning *best*. In the typical sense of the word, being optimistic means "expect the best possible outcome". A useful definition is offered by anthropologist Lionel Tiger, which defined optimism as "a mood or attitude associated with an expectation about the social or material future – one which the evaluator regards as socially desirable, to his [or her] advantage, or for his [or her] pleasure" (Tiger, 1979, p. 18).

In the literature, two conceptualisations of optimism are described: optimism as a personality trait, so-called dispositional optimism (i.e. a global expectation that more good things than bad will happen in the future) (Scheier et al., 1994) and optimism as an explanatory style (i.e. tendency to explain negative events by attributing the cause of these to external, specific factors; ex. attributing the failure of an exam to the wrong questions that came up) (Seligman, 1990).

In the late 1970s, some cognitive psychologists started accumulating evidence that psychologically healthy people are positively biased: for example, when speaking or writing, people tend to use more positive than negative words, they recall positive things sooner than negative ones, they evaluate themselves more positively than they evaluate others (Matlin & Stang, 1978). Taylor and colleagues argued that people's perceptions are optimistically biased and that human thinking is characterised by a robust positive bias, which promotes psychological well-being (Taylor & Brown, 1994). In fact, positive illusions are usually absent in people suffering from anxiety or depression, who display a more realistic or a pessimistic perception of the reality (Alloy & Abramson, 1979).

A growing number of studies focused on the origin of positive illusions as well as on their impact on physical and mental health.

Evidence from a variety of sources suggests that optimism is an inherent and highly beneficial psychological characteristic of human nature, linked to good mood and physical health. Tiger conceptualizes optimism as one of the most adaptive characteristic of human nature. He suggested that optimism pervades people's anticipation of the future and counteracts the fear linked to the anticipation of death, serving therefore an evolutionary function (Tiger, 1979).

Many studies indicated that optimism and positive illusions promote physical and psychological well-being. To this end, a recent study identified a relationship between optimistic expectancies and cell-mediated immunity (Segerstrom & Sephton, 2010). Optimistic expectancies of 124 law students were assessed with the use of a scale, including a range of cognitive expectancies (ex. "I will be less successful than most of my classmates"). Cell-mediated immunity (CMI) was measured by intradermal injection of DTH antigen preparation in each participant.

Within people, changes in optimistic expectancies were accompanied by changes in immunity. Some authors noted that dispositional optimism predicts better resistance to viral disease and cancer (Allison et al., 2003; Ironson et al., 2005).

Unrealistically positive views of the self, exaggerated perceptions of personal control and UO are some of the most studied positive illusions. These illusions serve a mental-health-promoting function and possibly make the world a "warmer and more active and beneficent place in which to live" (Taylor & Brown, 1988).

*The future will be great, especially for me* (Taylor & Brown, 1988)

UO refers to the common tendency of healthy people to systematically underestimate the likelihood that they will experience future misfortune, including illness (Weinstein, 1984; Weinstein, 1989). Weinstein originally reported this phenomenon. In his study, he observed that participants estimated their own chances of experiencing a variety of pleasant events, such getting a good salary or having a gifted child, as higher than those of their peers and their chance of experiencing negative events, such as contracting HIV infection or developing a drinking problem, as lower than the chances of their peers (Weinstein, 1980).

This mistaken belief is also designated with the term of "optimistic bias" or "illusion of invulnerability". As with many other kinds of positive illusions, UO is widespread and robust. Although most work focusing on the illusion of invulnerability related to health problems, this phenomenon is likely to emerge for a wide variety of positive

and negative events, independent of age and socioeconomic status of the sample (Fischer & Chalmers, 2008).
The tendency to view oneself as less likely than others in becoming ill or, more generally, to experiencing negative events is modulated by a series of factors. In the foreground are the motivational ones, in particular the need to protect self-esteem and to cope with unpredictability of life. Reducing anxiety, UO serves, like other positive illusions, a health-promoting function. This absence might indicate a bad affective state ("depressive realism") (Alloy & Abramson, 1979) or signal the presence of hypochondria (Barsky et al., 2001).

Optimistic attitudes are more likely to emerge from events that are perceived as controllable (Klein & Helweg-Larsen, 2002) and/or severe. Instead, illnesses previous experienced by the person usually lead to smaller bias (Weinstein, 1989). Besides motivational causes, positive illusions are encouraged and maintained by a series of cognitive errors. For example, the common tendency to compare themselves with a stereotype of a high-risk individual may also account for UO and induces to estimate its own risk factors as smaller than those of the peer-person to whom we are comparing (Chambers & Windschitl, 2004; Weinstein, 1989). Furthermore, when asked to compare their risk to that of others people, we tend to focus more on our own risk factors than on those of the peers, which result in a biased comparison (Chambers & Windschitl, 2004).

Although dispositional optimism is usually advantageous, it is important to notice that unrealistic biases can in some situations even be unfavourable. UO can lead to false beliefs that “all will be fine” and be associated with risky behavior (Dillard et al., 2009). We conclude therefore, as suggested by Sweeny and colleagues (2006, p. 305) that “People should be optimistic enough to take advantage of the many benefits of a positive outlook, but they should also sufficiently temper that optimism so that they can motivate preventative action and avoid being caught off guard”.

*Measurement*

One of the most popular tests for measuring dispositional optimism is the Life orientation test (LOT-R) (Scheier et al., 1994).

The attributional style questionnaire (ASQ) is based on the explanatory style definition of optimism. It lists positive and negative events and asks the participants to record a possible cause for the event (Peterson et al., 1982). Two methods are commonly used to establish unrealistic bias: the *direct method* and the *indirect method*. Using the *direct method*, a person is asked to estimate his risk relative to that of the average person of his age and sex on a scale that ranges from "below average" to "above average". If the mean response is lower than the midpoint one has demonstrated an optimistic bias.

Another approach is the so-called *indirect method*, which consists of asking the participant to make two judgments – an estimate of his own risk and an estimate of the risk of the average peer. These ratings will be subtracted, and if the mean difference is not zero, a bias exists. These methods are simple and widely used, however, they present some limits. Although they are effective to establish biases at a group level, they sometimes fail when trying to identify individual biases. In fact, a man who estimates his risk of lung cancer to be below average may be accurate if he has no risk factors for lung cancer. That is why it is necessary to develop new method able to accurately quantify optimistic bias at the individual level.

*Behavioral and neural correlates of UO*

In the last decades, researchers have mainly explored cognitive and motivational factors that contribute to unrealistic optimism. In this section, we will review some of the few studies interested in the brain processes underlying this widespread positive illusion.

In an experiment conducted in 1984, Drake found that participants induced to orient toward the right indicated greater personal optimism for future life events than those induced to orient toward the left (Drake, 1984).

A few years later, Drake & Ulrich (1992) exploited the line bisection task as measure of functional hemisphere predominance, to explore lateralization of unrealistic optimism. They asked 22 females and 28 males to bisect horizontal lines, after assessing their personal optimism degree. They found that the degree of line-bisecting error to the right - taken as a measure of LH predominance - was significantly related to the degree of personal optimism and that greater rightward bisecting errors predict greater optimism.

Drake's findings are in line with the theory of valence-dependent hemispheric processing of emotions, suggesting positive emotions to be primarily processed by anterior regions of the LH, while corresponding areas of the RH preferentially deal with negative stimuli (Davidson & Sutton, 1995). They also indicate that the cerebral hemispheres contribute to positive illusions in an asymmetrical manner.

In fact, observing clinical populations, we note that, as a rule, damage to anterior regions of the LH induces depression or even elicits "catastrophic reactions," while comparable damage to the RH may rather lead to enhanced positive mood, *anosodiaphoria* (i.e. marked downplaying of the consequences of an illness) and euphoric reactions (Davidson & Sutton, 1995; Gainotti, 1972; Silberman & Weingartner, 1986).

Clinical evidence and several research findings suggest that human cerebral hemispheres are asymmetrical involved in maintaining positive illusions and in particular, that UO results from LH relative dominance.

More recently, Sharot and colleagues conducted a neuroimaging study with the aim of elucidating how the brain generates an optimistic bias (Sharot et al., 2007). They analyzed functional magnetic resonance imaging scans from 15 young adults. During scanning, participants were invited to imagine emotionally arousing events like "the end of a romantic relationship" or "graduating". After the scanning session, subjects also completed an optimism scale. They found that when people imagined positive future events the activity in the rostral anterior cingulated cortex (rACC) and in the amygdala were most strongly correlated. Furthermore, they found that more optimistic people showed greater rACC activation when imagining positive versus negative future events than did less optimistic individuals. In other words, the rACC activation for positive events correlated with trait optimism. They concluded that these two regions are crucially involved in the tendency to engage in the projection of positive future events and speculate they could represent a possible brain basis for optimism. The results of this study are supported by findings from functional and structural neuroimaging of mood disorders: depressed patients showed in fact reduced volume and metabolism in the same subregion of the rACC that Sharot's group found correlated with optimism (Drevets, 2000).

Despite the growing interest toward the possible neural mechanism underlying positive illusions, at the present time, the neural basis for UO remains an open question.
We know, as pointed out by Sharot, that a malfunction of a neural pathway incorporating the rACC and the amygdala may cause depression (Drevets et al., 1997). However, if on one side, these regions may play a role in attention towards positive future events and away from negative ones, on the other side, a number of studies with clinical and healthy populations evidenced asymmetrical hemispheric involvement in emotions and positive illusions. Following these studies, UO would be mediated by LH mechanism.

*UO: a prospective anosognosia*

In our contributions (Chapter 2) we conceptualize UO regarding future health as a form of "prospective anosognosia", i.e. the non-pathological denial of health risks. We suggest that the evaluative process which enable healthy people to appraise their current physical and mental functioning and to detect dysfunction (i.e. nosognosia) is markedly biased towards an overly positive evaluation. We assume that a degree of anosognosia concerning one's own risk of future harm is normal and healthy and speculate that a qualitative similarity underspins *anosognosic denial* and *nosognosic optimism*. Proposing UO as a form of prospective anosognosia characterising the normal human functioning, we do not attempt to reduce anosognosia to a mere pathological exaggeration of unrealistic optimism; nonetheless, we believe that a similar neural mechanism underly healthy positive illusions and clinical anosognosia.

The recognition of a similarity between these two manifestations may open up new research avenues to the aim of identify the neural basis of anosognosia and optimism.

Our results on UO (reported in Chapter 2) emphasize the importance of an interhemispheric interaction to a realistic appraisal of one's self, being compatible with Ramachandran's model of anosognosia (Ramachandran, 1995). In his model, he identified the LH as the propagator of a healthy, normal image of the self and ascribed the right hemisphere the role of a "devil's advocate", which would detect any anomaly threatening this image.

Our findings in the context of optimism highlight the asymmetric involvement of the LH and RH in emotion regulation and self-evaluation and confirm the positive association between LH activity and positive emotions.

## 1.3 Brain lateralization of emotional processing

### 1.3.1 Four main theories

Emotion has not always been a popular topic for neuroscientists, in the same way we know it today. Thirty years ago the majority of studies focused on cognition, with relatively little research addressing emotion. Interest in emotion has increased exponentially during the last forty years, giving raise to a new discipline called "affective neuroscience" (Davidson & Sutton, 1995). Nowadays, the study of emotion has become a crucial target of research, essential for understanding a broad range of brain mechanisms.

During the past forty years, the field of affective neuroscience has debated the question of how the brain is organized to process emotions. More recently, technological advances such as dense-array electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) have allowed this investigation to more precisely identify the neural circuits that are involved in the experience of emotion and motivation. The two halves of the brain are considered to play different roles in emotional processing, but the specific contribution of each hemisphere continues to be debated.

I would like to emphasize the fact that the neural basis underlying behavioral complexity of emotion involves the entire nervous system. The experience of emotion relies on an intricate neural network, which involves different structures, among which the most important are prefrontal regions, cingulate gyrus, amygdala, hippocampus, parahippocampal gyrus, thalamus, hippothalamus, fornix (forming the "limbic system"), ventral tegmental area and septum. It is important to stress that all these structures interconnect intensively and none of them is solely responsible for any specific emotional state. However, some contribute more than others to this or that kind of emotion.

Many methods have been used for assessing the involvement of cerebral hemispheres in the processing of emotions. One of the earliest and most used methods is the divided visual field technique, introduced by Mishkin and Forgays in the fifties (1952). More recently, modern neuroimaging techniques such as fMRI, magnetoencephalography (MEG), EEG, and positron emission tomography (PET), have also permitted scientists to establish correlations between neurophysiologic activities and brain lateralization of emotional processing.

This chapter does not represent an exhaustive review of the huge literature dedicated to the study of emotion, nor will it provide a solid description of the neural pathways generating the affective experience. In the following pages, I will introduce the main theories concerning the cortical lateralization of emotional processing, providing a selection of findings from behavioral, EEG and fMRI studies.

*The right hemisphere model*

The right-hemisphere hypothesis posits that the RH is specialized for the perception, expression and experience of emotion, regardless of valence (Borod et al., 1998). Representing the oldest theory on brain asymmetry, it states that the LH is associated with cognitive processes, whereas the RH is rather concerned with emotional processing.
Early observations of a direct association between emotion processing and the RH were made nearly hundreds years ago. Subsequently, the RH hypothesis received further support by many behavioral and neuroimaging studies, which confirmed his validity. First of all, some studies indicated RH superiority for facial affect perception; this evidence led a group of researchers to argue that the RH may contain a “store of facial emotion representations” (Bowers & Heilman, 1984). Considerable experimental evidence supports this hypothesis. Tachistoscopic studies with healthy participants have demonstrated left visual field (RH) superiority for discriminating emotional faces (Landis et al., 1979). Studies of patients with unilateral cerebral lesions showed that patients with right-hemisphere damages perform worse than those with left-hemisphere lesions on tasks requiring the recognition or the discrimination of facial affect (Adolphs et al., 1996; Cicone et al., 1980). Further evidence comes from patients with split-brain syndrome. Benowitz and colleagues (1983) reported the case of a split-brain patient, who had no difficulty identifying

facial expressions when presented to the RH, but failed to identify the same facial expressions when presented to the LH. In a study using intracarotid sodium amytal injection, Ahern and colleagues (1991) found that affective faces are rated as less emotionally intense when shown to the anesthetized RH; conversely, this effect was not observed when faces were shown to the anesthetized LH. In addition, neuroimaging studies and electrophysiological recording lend support to this view. For instance, Narumoto and colleagues (2001) found that selective attention to facial emotion specifically enhanced activity within the right superior temporal sulcus, compared with attention to the face without regard to emotion.

In a review of seven studies involving brain-damaged patients, Borod (1993) indicated that patients with right brain damage are more frequently impaired in the expression of emotional prosody. Similarly, EEG studies found evidence of relative RH activation when participants were asked to generate emotional imagery (Karlin et al., 1979).

Emotional disorders have also been linked to increased activity of the RH. Mania has historically been associated with right anterior lesions (Gainotti, 1972) and Heller (1993) suggested depressive states to be associated with relatively increased right versus left anterior activity, but decreased right posterior activity.

*The valence model*

In contrast to studies which support overall RH dominance for perception and modulation of emotions, the valence model suggests that positive emotions are primarily processed by anterior regions of the LH, while corresponding areas of the RH preferentially deal with threatening, negative stimuli (Davidson & Sutton, 1995; Kinsbourne, 1978). The first line of evidence in favour of a valence-dependent hemispheric processing of emotions derives from clinical investigations of patients with unilateral brain damage. Damage to (anterior) regions of the LH often induces negative affect or depression, while comparable damage to the RH generally lead to enhanced positive mood, euphoric reactions or anosognosia for own disabilities (Gainotti, 1972). Patients with RH lesions have more difficulty perceiving negative versus positive emotion, whereas the perception of happy affective faces remains usually intact (Borod et al., 1997). A further demonstration of different emotional responses from the hemispheres comes from observation of patients undergoing the Wada test. Early intracarotid sodium amytal injection studies showed that injection at the left carotid artery induced "catastrophic reaction", leaving the subject to worry about the future, whereas injection at the right carotid artery produced euphoric reactions and sense of well-being (Silberman & Weingartner, 1986). Mood changes are supposed to result from the release of one hemisphere from inhibitory influences of the contralateral hemisphere: the RH, when not counterbalanced, would produce depression, while the unbalanced LH would produce euphoria. A study on a group of 150 patients experiencing visual hallucinations revealed that hallucinations are experienced as emotionally negative when occurring in the left visual field (LVF), while those in the right visual field (RVF) are of predominantly positive content (Walters et al., 2006).

Another strong support derives from research in animals. In fact, many studies demonstrated that across a vast range of species, threatening information appears more salient, when detected on the left of the animal's body (RH), whereas approach behavior is rather directed to the right side (LH). For instance, a horses' sensitivity to threat is larger when the aversive stimulus is presented on the left than on the right side (Austin & Rogers, 2007). Tail-wagging in dogs is modulated by the affective valence of the eliciting cue: right-biased for familiar stimuli such as the dog's owner and left-biased for threatening stimuli such as an unknown person or a dominant unfamiliar dog (Quaranta et al., 2007). Primate studies revealed a larger RH than LH arousal by the view of specifically aggressive acts (Parr & Hopkins, 2000). Even in reptilians and amphibia, lateral space seems to be associated with opposite emotive connotations; in toads, tongue protrusions are more frequently directed to the right during predatory behavior, but to the left when they signal agonistic acts (Vallortigara et al., 1998). Also early divided visual field studies in healthy subjects supported the valence model. Reuter-Lorenz and colleagues (1983) found that happy faces are identified quicker when presented within the RVF (LH), whereas sad faces within the LVF (RH). Another study showed that chimeric faces were more likely to be judged as positive when presented within the RVF (Natale et al., 1983).

However, results from lateralized tachistoscopic experiments are quite heterogeneous and only some of them produced support for the valence theory of emotional hemispheric processing (see the review by Habib, 1998). A variant of the valence theory postulates the existence of hemispheric specialization as a function of valence only for the expression of emotion (LH for positive and RH for negative emotions), whereas it considers the perception of both positive and negative affective stimuli to be a right cerebral function (Davidson, 1984).

*The approach-withdrawal model*

The approach-withdrawal model posits the existence of two separate systems of motivation and emotion—an approach and withdrawal systems (Davidson, 1992, 1998). These two systems are considered to be responsible for individual differences in reactivity to emotional stimuli, or "affective styles." With regard to this model, approach and withdrawal systems involve separate neural circuits of the frontal cortex. Emotions associated with approach behaviors (like happiness) are processed within left-anterior brain regions, whereas those associated with withdrawal behaviors (like fear) are processed within right-anterior regions. It is important to note that the prefrontal cortex is considered to be only one element of the approach and withdrawal systems . Other structures, in particular the basal ganglia and amygdala, are also believed to play crucial roles. Most positive emotions (like joy or pleasure) elicit approach behavior, whereas most negative emotions (like fear, disgust or shame) elicit withdrawal behavior. This is why this model is very similar to the valence model. Nonetheless, they disagree on the classification of the emotion of anger. Unlike other negative emotions, anger induces approach behavior.

Many studies provide empirical evidence supporting the approach-withdrawal model. For instance, Davidson and colleagues (Davidson et al., 1990) showed participants video recordings designed to elicit an approach (happiness) or withdrawal (disgust) emotion, and collected behavioral and EEG data corresponding to the stimuli. They found that the disgusting film was associated with a significant shift toward greater right relative to left frontal and anterior temporal arousal. Similarly, Coan and colleagues (2001) found that the production of withdrawal-related faces (e.g., fear, disgust) were associated with relatively less left frontal activation (as recorded via EEG).

A study conducted by Fox and colleagues (1995) demonstrated a relationship between resting frontal asymmetry and affective style. These authors correlated baseline frontal EEG asymmetry with social and interactive behaviors among forty-eight four-year-old children during free play. They found that children who exhibited greater left frontal arousal displayed greater social competence (e.g., approach behavior, social initiation and positive affect), while those exhibiting greater right frontal arousal evidenced greater social withdrawal (e.g. withdrawal behavior, social isolation).

This relationship has also found support in the adult population (Davidson, 1992a, 1992b, 1993; Davidson & Sutton, 1995). Studies of frontal asymmetry associated with feelings of anger have provided important experimental data in support of this model. Harmon-Jones & Allen (1998) demonstrated significant relationship between dispositional approach motivation elicited by anger and the anterior asymmetry in alpha activity. They found that dispositional anger is positively associated with left-anterior cortical activity but negatively associated with right-anterior cortical activity. Taken together, consistent findings from several studies suggest that the anterior asymmetry in cortical activity may reflect motivational direction rather than affective valence and confirm the validity of this model.

*The behavioral activation and inhibition (BAS/BIS) model*

The Behavioral Inhibition System (BIS) and the Behavioral Activation System (BAS) have been conceptualized as two neural motivational systems that regulate sensitivity to punishment and reward, respectively (Gray, 1990). This model posits that behavior and affect are controlled by activation of these two general motivational systems. Gray's model of emotion is based on evidence mostly from animal research supporting independent neurobiological mechanisms for these two systems. The appetitive system (BAS) activates behavior in response to signals of reward and nonpunishment, whereas the aversive system (BIS) inhibits behavior in response to signals of punishment and nonreward. Activation of the BAS is associated with positive feelings and approach behaviors, whereas activation of the BIS is associated with feelings of anxiety and avoidance behaviors (Gray, 1990). The BAS is predominantly mediated by dopaminergic pathways emanating from the ventral tegmental area to the nucleus accumbens and ventral striatum, while the BIS is controlled by serotonergic pathways from the raphe nucleus to septo-hippocampal systems (Depue & Iacono, 1989; Nothen et al., 1992).

Imbalance in BIS and BAS levels has been reported to be related to various forms of psychopathology (Scholten et al., 2006). Depression and mania appear to be associated with opposite BIS vs BAS profiles, stronger BIS than BAS in depression and stronger BAS than BIS in mania (Meyer et al., 1999). BAS activation is associated with positive feelings such as hope, whereas BIS activation is associated with negative feelings such as fear and anxiety, which induce freezing behavior. EEG technologies have allowed quantification of BAS and BIS lateralization strength. Recent EEG findings indicate that left and right frontal activity may reflect strength of the behavioral activation and behavioral inhibition systems, assessed using self-reported questionnaires. Persons with higher BAS scores display increased left frontal activation, whereas greater right frontal activation is evidenced in individuals with higher BIS scores (Allen et al., 2004; Sutton & Davidson, 1997). Interindividual frontal EEG arousal asymmetries related to differences in BIS and BAS levels has been confirmed by a number of studies.

The BIS/BAS scales are a cost- and time-effective instrument used to assess individual trait differences in human BIS and BAS levels (Carver & White, 1994).
They measure self-reported predispositions toward positive (approach) and negative (withdrawal) affect in response to generally rewarding or threatening situations. The questionnaire asks respondents to answer seven BIS-related questions (e.g., "I feel

worried when I think I have done poorly at something"), five BAS-reward responsiveness questions (e.g., "When I get something I want, I feel excited and energized"), four BAS-drive questions (e.g., "When I want something, I usually go all-out to get it"), and four BAS–fun seeking questions (e.g., "I will often do things for no other reason than that they might be fun"). The score reflects intraindividual BIS and BAS strenght, which is thought to be stable over time.

Diego and colleagues (2001) investigated the relationship between interaction style, EEG frontal asymmetry and BIS/BAS scores in sixty depressed mothers. They found that withdrawn and intrusive depressed mothers exhibit contralateral anterior brain activity and have opposite Behavioral Inhibition and Behavioral Approach profiles as reflected by BIS/BAS scale scores.

### 1.3.2 Open questions

Despite the new findings provided by many behavioral and lesion studies and the extensive progress made during the last four decades, our understanding of the cortical and subcortical lateralization of emotional processing is far from complete, and an enormous heterogeneity characterizes the results.

The valence model and the more recent approach-withdrawal hypothesis are similar and have received, over the last decades, the strongest support (Demaree et al., 2005). The BIS/BAS model is basically identical to the approach-withdrawal model but focuses on stable emotional traits (BIS and BAS strength) instead of states. Unlike the valence model, the BIS/BAS takes into account a relevant aspect of the evolution in which emotions are closely associated to the behavior of the individual in its environment. This model appears to be a better fit for the majority of data (e.g., anger).

Neuroimaging studies have supported the idea that the prefrontal cortex is a region of high affective asymmetry (Davidson & Sutton, 1995): the anterior portion of the LH is related to approach behaviors and positive affects, whereas the anterior region of the RH is associated with withdrawal behavior and negative affects. The left orbitofrontal areas are especially responsive to reward, whereas areas in the right orbitofrontal cortex are more involved during punishment (O'Doherty et al., 2001).

In contradiction to early models (Gainotti, 1972), the "dominance" of one hemisphere for emotional processing – as for other specific functions - is nowadays considered as relative and not absolute. Recent neuroimaging studies showed that small regions rather than whole hemispheres should be taken into account, when exploring lateralization of emotion. Although the investigaton of brain asymmetry associated with affective experience relies today on a more sophisticated level of anatomic specificity, it focuses mainly on the lateralization at a cortical level. Nonetheless, the contemplation of asymmetrical subcortical contributions to emotional processing is a critical aspect, often been disregarded, which should be incorporated to present cortical models (Gainotti et al., 1993). This would offer a more comprehensive appraisal of the brain basis of emotion as an experience that involves the whole brain. It is also important to remember that an emotional experience is a multifacet phenomenon, which involves at least two dimensions along two axes: *valence* (negative to positive) and *arousal* (low to high). Demaree and colleagues (2005) proposed a "three-factor" model, suggesting a third dimension called "dominance", a feelings of control over events versus feeling of being controlled.

Future studies should consider all different facets of the affective experience: pattern of brain asymmetry associated with valence, arousal and dominance need to be clarified and analysis of anatomic specificity should be put in the foreground. This would allow a better understanding of how activation of anterior brain regions produce different emotional experiences.

## 1.4 Goals of the present thesis

*Study 1*

The clinical evidence reviewed above (section 1.1) suggests the existence of functional hemispheric asymmetries in the appraisal of one's own illness. We have complained that the current research in anosognosia is too unilaterally focused on work with patients and the concept too much based solely on the *dys*functional aspects. We have reviewed the literature on unrealistic optimism in healthy persons and suggested to conceive this phenomenon as a form of "prospective anosognosia". The goal of study 1 is to test the validity of this proposal. Specifically, we aimed at investigating whether a physiological manipulation known to alleviate anosognosia in neurological patients (i.e. vestibular stimulation), would also reduce healthy participants' illusion of invulnerability to illness.

*Study 2 and 3*

A broad range of different experimental paradigms (reviewed in section 2.2) suggests a biological foundation of the association between lateral space exploration and the processing of emotional valence. However, the modulation of perception and exploration of space by emotional states and traits has produced mixed results.
While the purpose of study 2 is to examine perception of emotional stimuli as a function of interindividual differences in hemispatial attention, the purpose of study 3 is to manipulate hemispatial biases by a temporary induction of an emotional state.

# 2
# Own contributions

## 2.1 Nosognosia and unrealistic optimism

### 2.1.1 Study 1: Vestibular stimulation reduces unrealistic optimism

**Tamagni, C., Palla, A., Krummenacher, P., Vitacco, D., Huberle, E., Straumann, D., Hegemann, S., McKay, R., Brugger, P. (Nature Precedings, 2010)**

*Abstract*

UO refers to the tendency of healthy people to underestimate their risk of future misfortune. Just as left-ear caloric irrigation (CI) attenuates anosognosia (denial of manifest illness) in clinical patients, we found that it also reduces UO about future health risks in healthy individuals. This finding demonstrates asymmetric hemispheric involvement in emotion regulation and self-evaluation, and suggests that a similar neuropsychological process underpins anosognosia and healthy optimism.

*Introduction*

UO refers to the tendency of healthy people to systematically underestimate the likelihood that they will experience future misfortune, including illness (Weinstein, 1989). This phenomenon was originally reported by Weinstein, who observed that participants estimated their own chances of experiencing negative events, such as contracting lung cancer or developing a drinking problem, as lower than the chances of their peers (Weinstein, 1980). It is thought that this "illusion of invulnerability" derives mainly from the need to protect self-esteem and to cope with the fear of being harmed (Weinstein, 1989). Typically investigated in a social-psychological framework, we here postulate for the first time an association between this downplaying of threats to one's own health and the well-known clinical phenomenon of anosognosia, which involves denial or unawareness of manifest illness or impairment, spectacularly evidenced by some patients with predominantly RH temporo-parietal-insular lesions (Orfei et al., 2007). We specifically propose to conceptualize UO regarding future health as "prospective anosognosia", i.e. the non-pathological denial of health risks.

Left-ear CI with iced water is a potent means of stimulating the vestibular system. Beyond its contribution to orientation and physical balance, this system is also involved in maintaining one's emotional equilibrium (Ried & Aviles, 2007). In connection with the affective and cognitive evaluation of one's own health state, CI has been shown to temporarily alleviate anosognosic denial of left-sided paralysis (Cappa et al., 1987), to influence mood and to reduce manic symptoms (Dodson, 2004), presumably by boosting RH cortical networks subserving self-monitoring and insight. We therefore hypothesized that the same mechanism would transiently reduce UO about health risks in healthy individuals.

*Method*

Thirty-one healthy right-handed subjects (15 men, 20-40y) participated in this study. Prior to CI, each subject underwent an otological examination to ensure an intact tympanic membrane and, if necessary, to clear the external auditory canal. Subjects were then oriented in supine position with the head inclined 30° from the horizontal and cold water (24°C) was irrigated into the external auditory canal first of one, then of the other ear (Fitzgerald & Hallpike, 1942). Eye movement recordings with video-oculography verified successful vestibular stimulation. 30 seconds after CI of each ear was initiated, participants were asked to estimate their own risk, relative to that of their peers (same age, sex and education), of contracting a series of illnesses. Thirty illnesses (Table 4) were selected from a larger pool and pre-rated for the present study by a group of 30 independent healthy participants. To adapt our stimuli to the within-subjects design, we used three different lists of illnesses (one per condition) carefully matched with respect to harmfulness ($F(2,27) = .05$, $p = .951$), word length ($F(2,27) = .17$, $p = .845$), frequency ($F(2,27) = .08$, $p = .923$), avoidability ($F(2,27) = .61$, $p = .551$), and own experience and exposure ($F(2,27) = .06$, $p = .942$). The average level of UO per condition (baseline with no CI, left-ear CI and right-ear CI; order counterbalanced) was calculated for each participant.

CI continued throughout the risk-estimation period. The risk rating scale ranged from -6 (lower risk) to +6 (higher risk). Each participant was tested in three conditions, with 5 minutes rest between each: baseline with no CI (always first), left-ear CI and right-ear CI (order counterbalanced). Average UO per condition (mean of 10 ratings) was calculated for each participant.

**Table 4: List of illnesses read to the subjects (English translation in parentheses)**

| Block 1 | Block 2 | Block 3 |
|---|---|---|
| Pest<br>(pest) | Krebs<br>(cancer) | AIDS<br>(AIDS) |
| Lepra<br>(leprosy) | Pocken<br>(smallpox) | Grippe<br>(flue) |
| Rheuma<br>(rheumatism) | Anthrax<br>(anthrax) | Thyphus<br>(typhus) |
| Angina<br>(angina) | Migräne<br>(migraine) | Syphilis<br>(syphilis) |
| Malaria<br>(malaria) | Epilepsie<br>(epilepsy) | Hirntumor<br>(brain tumor) |
| Diabetes<br>(diabetes) | Rinderwahn<br>(mad cow disease) | Gelbsucht<br>(jaundice) |
| Depression<br>(depression) | Tuberkulose<br>(tuberculosis) | Arthritis<br>(arthritis) |
| Herzinfarkt<br>(heart attack) | Nierenleiden<br>(renal disease) | Schizophrenie<br>(schizophrenia) |
| Lungenentzündung<br>(pneumonia) | Magengeschwür<br>(stomach ulcer) | Multiple Sklerose<br>(multiple sclerosis) |
| Blinddarmentzündung<br>(appendicitis) | Hirnhautentzündung<br>(meningitis) | Mittelohrentzündung<br>(acute ear infection) |

**Table 5: Experimental design of study 1**

| | Variables | Levels | Operationalization |
|---|---|---|---|
| **Independent variables** | Caloric irrigation | Baseline<br>Left<br>Right | |
| **Dependent variables** | Average UO | | Mean of 10 ratings per condition was calculated for each |

*Results*

A two-way mixed-design ANOVA, with gender as between-subjects variable and condition (baseline, left, right) as within-subjects variable, revealed a significant main effect of condition on the magnitude of average UO ($F(30)=3.5$, p=0.036). Compared to baseline, average UO was significantly lower during left-ear CI ($t(30)=3.0$; $p=.016$), whereas it remained unchanged during right-ear CI ($t(30)=1.44.$, $p=.476$) (Fig. 4a). Subjects' UO was thus reduced selectively after left-ear stimulation.

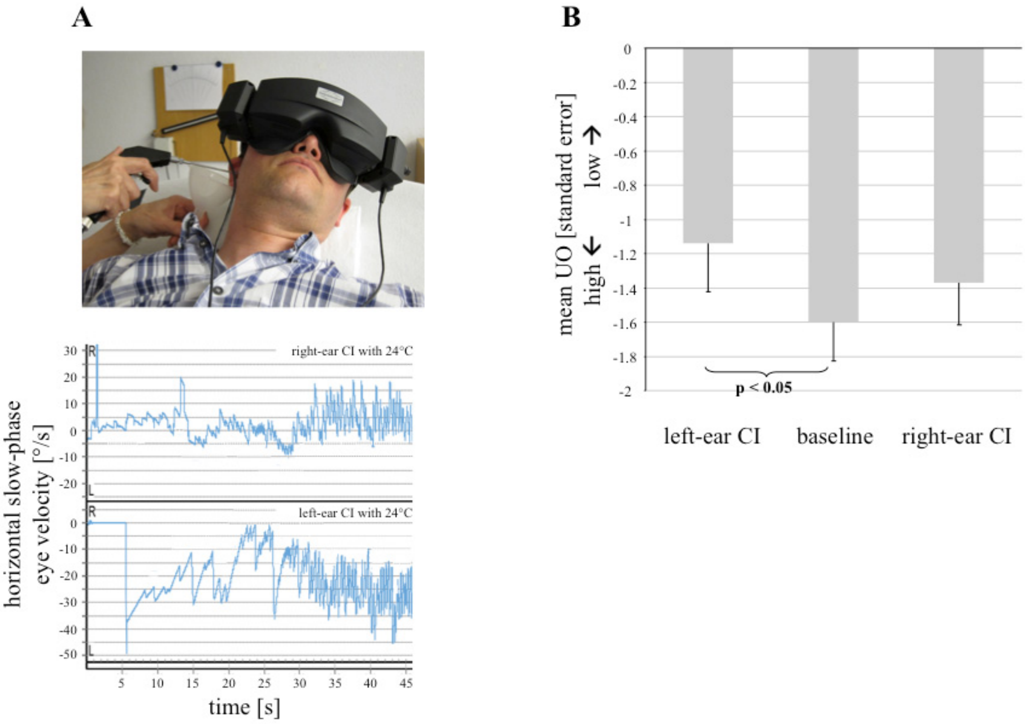


**Figure 4: (a) Right-ear cold-water (24°C) CI in one typical subject.** Note the similar strength of nystagmus, quantified by the eye movement velocity during the nystagmic slow-phase, for right- (60°/s) and left-ear (55°/s) CI (lower panel). Over all subjects, nystagmus during right-ear CI (mean ± SEM: 28.7°/s ± 2.5) was not significantly different from that during left-ear CI (27.6°/s ± 2.8; paired t-test: p=0.56). UO assessment started after 30 seconds of CI. Nystagmus was present throughout the risk-estimation period. **(b) Magnitude of average UO under left-ear CI, baseline and right-ear CI.** Compared to baseline (mean ± SEM: -1.62 ± 0.23), UO was reduced under left-ear cold-water CI (-1.22 ± 0.28). No comparable effect was found during right-ear CI (-1.42 ± 0.26).

*Discussion*

Cold-water CI of the ears predominantly activates brain areas in the contralateral hemisphere, in particular the parieto-insular cortex, which is considered the ‘core region’ of the multisensory vestibular cortex (Guldin & Grusser, 1998). In the RH, these regions also play a crucial role in self-awareness and their impairment may lead to anosognosia (Craig, 2009; Orfei et al., 2007). The finding that left-ear CI reduces UO in healthy subjects, possibly through activation of the right cerebral hemisphere, corroborates a neural basis of UO (Sharot et al., 2007) and supports our hypothesis that a qualitatively similar neuropsychological process underpins anosognosia and healthy optimism. Notably, this reduction is already present with a moderate vestibular stimulation (24° C). Presumably iced water would have produced a larger effect. However, since ice-water irrigation causes nausea in many subjects, we opted for the weaker stimulus. We speculate that the absence of an increase in UO during right-ear CI is linked to the larger vestibular responsivity of the RH (Bottini et al., 1994; Dieterich et al., 2003) and the reportedly strong ipsilateral activation after cold water irrigation of the right ear (Suzuki et al., 2001).

The conceptualization of a person’s underestimation of future health risks as “prospective anosognosia” may open up new research avenues bridging the gap between neurology and psychology. It enables the investigation of nosognosia as a continuum function, ranging from the “hypernosognosia” of conversion disorders, through the unrealistic pessimism of the hypochondriac (Barsky et al., 2001), to healthy optimism and its pathological exaggeration in the overt denial of illness. Our findings highlight the asymmetric involvement of the left and right hemispheres in emotion regulation and realistic self-evaluation. They identify the RH parieto-insular cortex as a core region for the evaluation of one’s well-being and the anticipatory awareness of one’s future state (Craig, 2009). The human capacity to perceive the present and to project one’s self into the future may rely on a delicate functional balance between the two cerebral hemispheres.

## 2.2 Interaction between emotion and space

### 2.2.1 Study 2: Emotion and space: lateralized emotional word detection depends on line bisection bias

**Tamagni, C., Mantei, T; Brugger, P. (Neuroscience, 2009)**

*Abstract*

There is converging evidence, from various independent areas of neuroscience, for a functional specialization of the left and right cerebral hemispheres for positive and negative emotions, respectively ("valence theory" of emotional processing). One subfield, however, has produced mixed results, i.e. work on the detection of parafoveally presented positively or negatively emotional words by healthy subjects. RVF or LVF advantages were described and interpreted as reflecting the superiority of either the LH for linguistic material, or of the RH for highly emotional stimuli. Here we show that 48 healthy, right-handed participants' performance on a lateralized lexical decision task depends on their individual inclination to bisect a line to the left or right of the objective center. Only those with a bisection bias to the right showed the LH advantage for word detection known from the neuropsychological literature. Negative emotional words were processed with comparable accuracy in the two visual fields. However, a recognition advantage for negative over positive emotional words was found exclusively for those participants with a leftward line bisection bias. These results suggest that in work on functional hemispheric differences state variables like stimulus lateralization and word emotionality may be less decisive than the trait variable of lateral hemispatial attention. We propose a cautious reconsideration of the concept of "hemisphericity", which once emphasized individual differences in baseline hemispheric arousal, but was later dismissed in a reaction to oversimplifications in popular science accounts.

*Introduction*

An influential theory of emotion processing suggests that approach-related, positive emotions are primarily processed by anterior regions of the LH, while corresponding areas of the RH preferentially deal with threatening, withdrawal-related stimuli (Davidson & Sutton, 1995; Kinsbourne, 1978). Support for this "valence theory" of emotional hemispheric processing comes from at least four largely independent areas of research.

First, anthropological sources have long pointed out an association, culturally largely invariant, between "right" and "correct", "good" and "favorable" and between "left" and "depraved", "sinister" or "gauche", respectively (Hertz, 1909). This association is not likely to be due to peripheral factors like manual dexterity and skill, but rather reflects a more general tendency to expect safety in the right hemispace and danger on one's left (Fabbro, 1994; Tan, 1998). Whether these expectations are based directly on (unilateral) neural networks common to the analysis of both space and emotions or whether they reflect more abstract congruency effects in the frame of a metaphorical representation of affect (Crawford et al., 2006; Meier & Robinson, 2005) is currently a matter of debate.

A second line of evidence in favour of a valence-dependent hemispheric processing of emotions derives from clinical investigations of patients with unilateral brain damage. As a rule, damage to (anterior) regions of the LH induces negative affect, depression or even elicits "catastrophic reactions", while comparable damage to the RH may rather lead to enhanced positive mood, anosodiaphoria (i.e., marked downplaying of the consequences of an illness) and mania-like, euphoric reactions (Davidson & Sutton, 1995; Gainotti, 1972; Silberman & Weingartner, 1986). Also, unilateral hallucinations after brain damage are experienced as emotionally negative when occurring in the LVF, while those in the RVF are of predominantly positive content (Walters et al., 2006). Even in not strictly lateralized psychiatric disorders, the degree of negativity of hallucinatory experiences correlates with specifically RH involvement, both in the auditory-verbal (Sommer et al., 2008) and somesthetic domain (Brugger, 2007).

Third, the perhaps strongest support for a biological foundation of the association between lateral space and emotional valence derives from research in animals. Primate studies revealed a larger RH than LH arousal by the view of specifically aggressive acts (Parr & Hopkins, 2000) and, on the output side, more aggressive displays to enemies approaching from the *left* hemispace (Casperd & Dunbar, 1996). Horses' sensitivity to threat is larger when the aversive stimulus is presented on the left than on the right side (Austin & Rogers, 2007), and tail-wagging in dogs is modulated by the affective valence of the eliciting cue: right-biased for familiar stimuli such as the dog's owner and left-biased for threatening stimuli such as an unknown conspecific (Quaranta et al., 2007). Even in reptilians and amphibia, lateral space seems to be associated with opposite emotive connotations; in toads, tongue protrusions are more frequently directed to the right during predatory behavior, but to the left when they signal agonistic acts (Vallortigara et al., 1998). In lizards, the finding that specifically aggressive behavior is under left eye/RH guidance made (Deckel, 1995) p. 194 conclude: "...these results suggest that the lizard *Anolis*, like humans, rats, and chicks, may mediate aggressive responses predominantly through right-hemispheric mechanisms".

Finally, divided visual field studies in healthy subjects revealed a RH superiority in the recognition of negative facial expressions and a similar superiority of the LH for happy expressions (Reuter-Lorenz & Davidson, 1981). In contrast, lateralized tachistoscopic experiments with *verbal* stimuli have produced mixed support for the valence theory of emotional hemispheric processing (see the review by (Habib, 1998) In some studies, emotional words were better recognized in the LVF/RH, irrespective of valence (Graves et al., 1981). Other authors have found a perceptual identification advantage for the RVF, reflecting the dominance of the LH for linguistic processing (Nagae & Moscovitch, 2002). Because of these inconsistencies, valence theories are usually discussed as only one of several alternatives in the conceptual analysis of hemispheric differences in emotional processing (see Demaree et al., 2005), for a comprehensive overview).

To our knowledge, in none of the previous experiments on the lateralized tachistoscopic detection of highly emotional words performances were ever analyzed as a function of a subject's baseline asymmetry in hemispatial attention. In line bisection tasks, for instance, lateral deviations of the subjective midpoint to either the left or right side are a robust indicator of hemispheric involvement also in non-spatial cognition (Mohr et al., 2003; Taylor et al., 2002). With special reference to emotional processing, Drake & Ulrich (1992) found right-handed subjects, who showed a rightward displacement in line bisection (reflecting a LH mediated orienting response), more optimistic than those showing a displacement to the opposite side of the lines' objective midpoint. The purpose of the present experiment was to measure detection performance for highly emotional words not only as a function of the visual field / hemisphere of presentation (a state variable), but also as a function of an individual's hemispatial line bisection bias as a trait.

*Experimental procedures*

Forty-eight healthy university students (24 women) gave written informed consent to participate in the experiment. Testing was undertaken in accordance with the Declaration of Helsinki and the local Ethics Committee had approved the study. Participants' mean age was 24.5 years (SD=1.3 yrs.), all were neurologically and psychiatrically healthy according to an extended neuropsychiatric history interview, had normal or corrected-to-normal vision and were strongly right-handed (Chapman & Chapman, 1987).

The word detection task consisted of 64 trials. In each trial, a letter string (3 to 7 letters) was flashed for 116 msec either to the left or to the right of a central fixation cross, which had to be fixated by subjects for the entire task (stimulus excentricity was 2 to 4 degrees of visual angle horizontally). In 32 trials, the letter string was a pronounceable nonsense word (no response required), in 32 trials it was either a positively (16 trials) or negatively emotional word (keyboard response "as fast as possible" with a response key ipsilateral to the flashed word; instructions did not mention word emotionality as a critical factor). Stimulus words were taken from a list of words previously rated as unambiguously eliciting highly positive or highly negative emotions by a large independent student group (Gianotti et al., 2008). The full list of stimulus words can be found below. Each emotional word was once presented in the RVF and once in the LVF, the sequence of visual field stimulation was pseudorandomized. Stimulus presentation and response collection was programmed with the software MacProbe (Hunt, 1994).

The line bisection task required subjects to mark the midpoint of each of 12 lines (line lengths 13-24.5 cm) with a sharp pencil held in the dominant right hand. Displacements of the subjective from the objective midpoint were measured to the nearest mm for each line, and the average displacement over all 12 lines was calculated for each participant. Based on the direction of the mean displacement (left or right of objective midpoint), a subject was ascribed to one of two bisection groups ("left bisectors" or "right bisectors").

We planned to perform an ANOVA of the number of correct word detections with two between-subject factors (gender and bisection group) and visual field/hemisphere and valence of word emotionality as repeated measures. We also planned to correlate individual displacements in the bisection task with the number of correctly detected words (positive and negative) in each visual field. Emphasis was not on the absolute error in bisection, but on its direction (i.e. leftward vs. rightward bisections).

Target stimuli of the word detection task were following:

Positively emotional words: GLÜCK (happiness); HERZ (heart); KUSS (kiss); LEBEN (life); LIEBE (love); LUST (zest, lust); SPASS (fun); WONNE (delight)

Negatively emotional words: ANGST (fear); GIFT (poison); GRAB (grave); HASS (hatred); MORD (murder); PANIK (panic); SARG (coffin); TOD (death)

**Table 6: Experimental design of study 2**

| | Variables | Levels | Operationalization |
|---|---|---|---|
| **Independent variables** | Visual field<br><br>Word valence | Left<br>Right<br><br>Positive<br>Negative<br>None | |
| **Dependent variables** | Word detection accuracy<br><br>Average deviation from mid-line | | Calculation of the number of correct word detections for each participant<br><br>Calculation of the average displacement in mm over all 12 horizontal lines for each participant |

*Results*

Twenty-nine subjects (13 women) were left bisectors, 18 right bisectors. The average bisection performance of one participant (a woman) was exactly at the objective midpoint, and her word detection performance was not analyzed.

The planned ANOVA of correct word detections revealed main effects of visual field ($F = 11.5$, $p < .002$) and valence ($F = 17.0$, $p < .0005$); words in the RVF/LH were better detected than in the LVF/RH and negative words were better recognized than positive words. There were no main effects of gender ($F =.44$, $p>.51$) and bisection group ($F = .038$, $p>.84$), but significant interactions between bisection group and visual field ($F = 4.9$, $p < .04$) and valence ($F = 9.1$, $p<.005$). Participants of the right bisection group had a strong RVF/LH superiority for correct word detections (paired t-test, $t=3.3$, $p<.005$, two-tailed; see Figure 5) while there was no visual field/hemisphere superiority for the participants of the left bisection group ($t=1.1$, p=.30; Figure 5). Only left bisectors detected more negatively than positively valenced words (paired t-test, t=5.2, p<.0001, two-tailed; see Figure 6); there was no comparable difference for right bisectors (t=1.1, p=.30, two-tailed; Figure 6). Gender did not interact with any of the other factors (all F-values ≤ 2.3, corresponding p-values >.13). Individual deviations in the bisection task (mean over 12 lines) correlated positively with the number of correctly recognized positive emotional words in the RVF/LH (r=.30, p<.05, two-tailed; the more rightward the displacement, the better the detection), but tendentially negatively with the number of negative emotional words in the LVF/RH (r=-.23, p=.12, two-tailed; the more rightward the displacement, the poorer the detection). Both these correlations were clearly significant for the 24 men (r=.52, p<.01, two-tailed and r=-.44, p<.05, two-tailed), but not for the women (both r-values <.16).

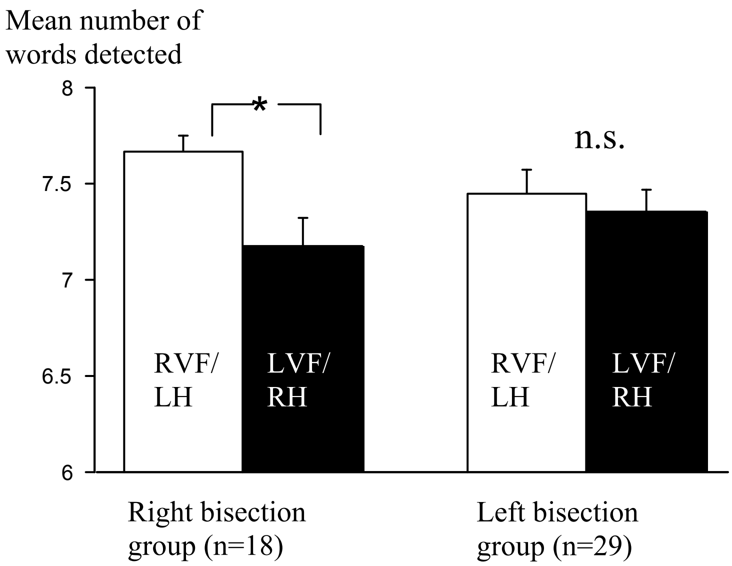


**Figure 5: Mean correct word detections irrespective of emotional valence (max. possible = 8.0 per visual field).** Data are displayed for two participant groups separately, according to their inclination to bisect lines to the left or right of the true center. A RVF/ LH superiority is only evident for participants with a rightward bisection bias. Error bars are standard errors of the mean.

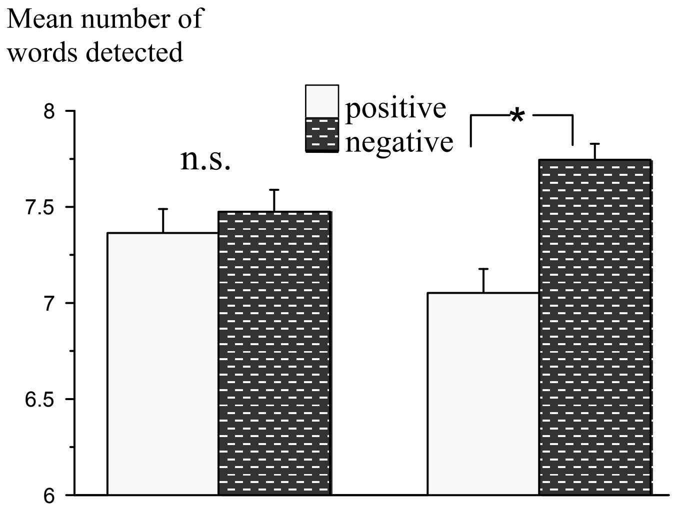


**Figure 6: Mean correct word detections (max. possible = 8.0) as a function of emotional valence.** Data are displayed for two participant groups separately, according to their inclination to bisect lines to the left or right of the true center. A recognition advantage for negatively emotional words is only evident for participants with a leftward bisection bias. Error bars are standard errors of the mean.

*Discussion*

We assessed healthy right-handed subjects' detection accuracy for highly emotional words presented in the RVF or LVF, that is, projecting primarily to the LH or RH, respectively. Half of the words elicited positive emotions (e.g., KISS), the other half negative emotions (e.g., MURDER). In the past, similar experiments with nonverbal stimuli (e.g. photographs of faces or scenes) had revealed an interaction between visual field of presentation and emotional valence, specifically a better performance of the LH for positive and a better performance of the RH for negative emotions (Reuter-Lorenz & Davidson, 1981). However, lexical decision experiments have often failed to find such an interaction between the valence of a stimulus word and the processing hemisphere (Graves et al., 1981; Nagae & Moscovitch, 2002). Based on known effects of an individual's hemispatial bias on cognitive processing (Mohr et al., 2003; Taylor et al., 2002) and emotional attitudes (Drake & Ulrich, 1992), we assessed our subjects' inclination to bisect a line to the left or right of its veridical midpoint. We ascribed a participant to a right or a left bisection group depending on whether his or her bisection mark (averaged over 12 trials) deviated to either side. The fact that the majority of our subjects deviated to the left is in accordance with a vast literature on "pseudoneglect", i.e. the predominant tendency towards systematic leftward shifts of spatial attention both in healthy humans (Jewell & McCourt, 2000) and animals (Diekamp et al., 2005). The magnitude of pseudoneglect is thought to be a function of the extent to which an individual relies on RH cognitive functions, both spatial and non-spatial (Taylor et al., 2002). In fact, as a group, our left bisecting subjects did not show the LH superiority for lexical decisions regularly described for right-handed subjects in the neuropsychological literature. This lack of dominance was due to both a numerically diminished RVF/LH performance, and a similarly *enhanced* detection accuracy for the LVF/RH (Figure 5), lending support to the model of interhemispheric cooperation based on a mechanism of mutual inhibition and release (Regard et al., 1994). With respect to the emotional valence of the stimulus words, a line bisection bias towards the left was accompanied by a significantly better detection accuracy for negative compared to positive words; no comparable asymmetry was observed in the subjects of the right-bisection group. This LVF advantage evidenced by the left bisectors is in accordance with previous lesion studies, which emphasized the RH's prominent role in the experience of specifically negative emotions. Such a role was inferred from the observation that patients with right-sided cortical damage were more likely to show an elevated, positive mood and a neglect, not only of the left half of space, but also of the severity of their symptoms (Davidson & Sutton, 1995). However, single-system models like the valence theory of hemispheric processing or one of its major rival concepts, the general RH superiority for all emotional experience, have received but limited support from neuroimaging studies (Murphy et al., 2003). These have rather implicated complex interaction between cortical (anterior and posterior) and subcortical structures in the mediation of both the perception and the production of emotions. We suggest that future neuroimaging experiments could profit from the findings in the present experiment. An assessment of individual subjects' baseline lateral activation asymmetries in anterior cortical circuits could enable researchers to avoid the often bewildering multiplicity of activation areas in response to even rather focal task demands. Paying attention to the issue of individual differences could help to reduce the variance across participants and lead to entirely new insights into the functional neuroanatomy of emotion.

In previous decades, individual differences in baseline hemispheric activation states were captured by the concept of "hemisphericity" (Bogen et al., 1972). Unfortunately, this concept of hemispheric balance *as a trait* became soon a victim of the then rapid popularization of research in functional hemispheric specialization. It deteriorated to pop-psychological accounts of "left brain types" and "right brain types". As a consequence, the notion of hemisphericity was discredited in the scientific literature (Beaumont et al., 1984). We suggest that this reaction of academic neuropsychologists was unwarranted and may have prevented consideration of individual differences in baseline hemispheric arousal. Specifically, it is conceivable that previous failures to substantiate the valence theory of emotional processing in experimental paradigms involving lateralized lexical decisions may have been due to a unilateral emphasis on the visual field of word presentation. Our results show that this state-variable of hemifield-hemisphere association may be less decisive than a person's inclination, as a trait, to process space and unilaterally presented stimuli with a relative preference for using one hemisphere more than the other. This notion is in accordance with earlier observations that baseline arousal differences between the hemispheres predicted subjects' performances in a wide variety of lateralized perceptual decision tasks (Kim & Levine, 1992; Levy et al., 1983; Spencer & Banich, 2005).

On a more general level, our finding of an interaction between emotion and space adds to a growing literature on tight relationships between affective states and indicators of spatial position. Phrases like "a close friend" or "distant acquaintances" are sayings, whose emotional connotations can be traced to the processing of near and far space. Positively valued words are reportedly faster recognized when their presentation on a screen induces the illusion of an approaching movement, while words depicting negative emotions are better detected when they seem to move away from oneself (Neumann & Strack, 2000). Also in the horizontal dimension, motion and emotion can intimately influence each other. For instance, the error of pointing to the location where a moving stimulus has just vanished (in the direction of movement, "representational momentum") is exaggerated by an emotionally attractive relationship between the moving object and a laterally presented flanker (e.g. a mouse and a cheese). On the other hand, a threatening flanker (a cat, in the case of a moving mouse) diminishes the error by counteracting the past-pointing (Daum & Frick, 2004). Future research should elucidate left/right asymmetries in such instances of embodied cognition and try to disentangle metaphorical (i.e. linguistically mediated) components of spatial-emotional congruency effects from more hard-wired, biologically founded links between emotion and space.

### 2.2.2 Study 3: Contemplating negative events shifts attention to the left

**Tamagni, C., Croce, S., Wettstein, V., Brugger, P. (Submitted to CABN, 2010)**

*Abstract*

We provide a review of studies investigating the interactions between emotional processing and spatial attention (along the horizontal, radial and vertical axis).
We also introduce an experiment, which required adults and children to bisect horizontal and radial lines while contemplating positive or negative events. Imagining negative events enhanced leftward deviation in both groups, with an overall larger bisection error in children. No difference in positive and negative emotion conditions emerged for radial bisections. The findings in the horizontal dimension are consistent with the previous literature and corroborate the predominant role of the RH in mediating negative affect. The failure to modulate the attentional bias along the radial axis is interpreted as pointing to a more metaphorical representation of affect in connection with the concepts "near" and "far".

*Introduction*

Links between emotion and space abound in our daily lives, even if we may rarely get aware of them at a conscious level. In language, they hide in words with a double-meaning, one designating a spatial direction or extension, the other having an affective connotation (*right*, *great*). They also lure in a wide range of common metaphors, which for instance represent affective involvement in terms of distance (a *close* friend, a *distant* relative) or affective valence in terms of verticality (*thumbs up/down*; *sinking into depression*; showing *elevated mood*). A rapidly growing body of empirical data shows that these space-affect associations do not simply reflect superficial linguistic conventions, but play a central role in the organization of thought (Barsalou, 2008; Crawford et al., 2006).

Tables 7-9 provide a selective overview on studies documenting the tight interplay between emotional processing and spatial orientation along, respectively, the three cardinal axes left/right, near/far and up/down.

*Affect and attention along the lateral horizontal extension (Tab. 7)*

The left/right dimension is probably the one most intimately linked to emotional processing. This may be the consequence of a hardwired specialization of each cerebral hemisphere for dealing with information incoming from the contralateral hemispace, which coincides with a similar specialization for stimuli that have a positive or negative emotional valence. This laterality aspect of emotion and space appears to be deeply engraved into bilaterally symmetric nervous systems. Thus, the idea that positive affect is associated with the right side of space and negative affect with the left hemispace abounds in studies on animal laterality (MacNeilage et al., 2009). Across a vast range of species, threatening information appears more salient, when detected on the left of the animal's body and approach-signalling behavior is rather directed to the right side. In human neuropsychology, "valence theories" of emotional hemispheric processing (Demaree et al., 2005; Kinsbourne, 1978) describe an association between positive affect and the LH and an association between negative affect and the RH. Much of the evidence for these opposite emotional hemispheric preferences comes from clinical observations in patients with unilateral brain lesions. Thus, depression often follows (anterior) damage to LH cortical structures, whereas mania or inappropriately elevated mood is more frequent after right-sided lesions (Gainotti, 1972). Work with healthy subjects complements these inferences from patient observation. Thus, divided visual field experiments revealed a recognition superiority of the LH for happy facial expression and a similar advantage of the RH for sad expressions (Davidson & Sutton, 1995; Reuter-Lorenz & Davidson, 1981). Likewise, in a study on lateral hemispatial asymmetries as a trait, right-handed subjects with a marked left-sided displacement in line bisection ("pseudoneglect") showed a recognition advantage for negative over positive emotional words (Tamagni et al., 2009).

In Table 7 we list studies which have investigated interactions between healthy subjects' hemispatial bias and their affective state or the emotional valence of a stimulus. Not included are lateralized tachistoscopic or dichotic experiments as typically designed to test classical valence theories of emotional hemispheric processing. Otherwise, we have attempted to select a broad range of different experimental paradigms, without however, claiming to be exhaustive. Some of these paradigms aimed at biasing the emotional evaluation of neutral stimuli by asymmetric spatial orientation. Drake (1987), for instance, long before the term "embodied cognition" was fashionable, had participants turn their body to one side of space and indicate how much they liked or disliked photographs of outdoor scenes taken from a magazine (Tab. 7). He found that male subjects liked right-sided pictures better than left-sided, and ascribed the absence of a similarly significant effect in the female subjects to insufficient statistical power. More recently, one would have accounted for this gender effect in terms of gender differences in hemispheric cooperation (Cahill, 2006). Other experimenters used sensory stimulation of one side of the body to bias aesthetic judgments or emotionality ratings. Bassel & Schiff (2001), for instance, found that subjects, who had received right-sided vibrotactile stimulation to the forearm during approx. half an hour, made more positive judgments of an emotionally neutral film than those after left-sided stimulation (Tab. 7). Similar results were obtained after unilateral motor action, such as the contraction of the hand (Schiff & Truchon, 1993) or facial muscles (Schiff & Lamon, 1994).

Root and colleagues (2006) asked participants to identify the emotion of target faces responding with either the left or the right hand. Right-hand responses were faster for happy faces, whereas left-hand responses were faster for angry faces, a result which supports the view that response preparation to positive stimuli is left-lateralized.

A unique approach was described by Wapner and colleagues (1956), who studied the effect of danger to participants' left or right side on lateral shifts of spatial attention (Tab. 7). As they were not interested in left/right differences, they did not discuss the laterality finding that emerged from their manipulation. Only those subjects standing on the *left* edge of a table, thus having the threatening stimulus of a "precipice" to their left, showed a right-sided attentional shift in their subjective straight ahead.

More modern authors, applying comparable paradigms of unilaterally applied threat stimuli in animal research (e.g., Austin & Rogers, 2007) would have interpreted this finding as a superiority of the RH in detecting danger. We note, however, that such an interpretation is at variance with the finding of an enhanced *right*-sided spatial attention, in the study by Wapner et al., as a consequence of the presumably larger RH activation.

The bisection of horizontally presented lines is another paradigm used in studies on emotional-spatial interactions. Used primarily as a clinical tool to quantify motor and attentional biases in brain damaged patients, line bisection can be exploited to monitor a surprising number of cognitive operations (Fischer, 2001). A pioneer application in the domain of emotional processing is the study by Drake and Ulrich, 1992 (Exp. 2; see Tab. 7). These authors assessed participants' "personal optimism", i.e. their tendency to overestimate the likelihood of positive events (e.g., getting a higher salary) and to underestimate the likelihood of negative events (e.g., getting divorced). Event probabilities had to be estimated for one's own future life and in comparison to the probabilities assumed for a typical peer (same sex, age, socioeconomic background, etc.). Optimism scores were positively correlated to right-deviations in a line bisection task, a finding interpreted as favoring the view of a LH dominance for supporting a positive emotional attitude. Also Drago et al. (2008) had their subjects bisect lines after the judgment of emotional valence of a series of paintings (Tab. 7). They used participants' accuracy of horizontal line bisection performance, irrespective of the lateral deviation of the errors, to predict differences in emotion evocation. Findings indicated that people, who display a greater accuracy in the line bisection task (i.e. greater ability to allocate attention) judge the evocative impact of paintings to be greater, suggesting that line bisection performance reflect that interindividual differences in emotional processing. The results also showed that right temporo-parietal regions are critical for both spatial attention and emotional processing.

A novel method was employed by Foster et al. (2008), who studied attentional allocation along two dimensions at once, i.e. in the lateral horizontal and in the radial extension (see Tab. 7 and Tab. 8). They required participants to distribute pegs marked with an emotional label on a large board “in any position of their chosing”. Labels were “happy”, “joyful”, “surprised”, “afraid”, “sad”, and “disgusted”. Only the first three of them, i.e. the positively labelled pegs, were placed with a significant lateral and radial bias. Contrary to predictions from classical valence theories of emotional hemispheric processing, there was a left-sided preference for the positive emotions. This finding was interpreted by the authors as a release of posterior right hemispheric functions as a consequence of a left posterior inhibition, the latter itself a result of emotion-induced left anterior activation. Apart from this experiment, the ambiguous finding by Wapner et al. (1956) and the null results by Crawford et al. (2006), the studies listed in Table 7 provide support for the contention of an association of positive affect with the right side of space and a left-sided spatial bias for negative affect.

**Table 7: Synopsis of 9 experiments on interactions between healthy human subjects' emotional processing and attention along the left/right axis**

| **Reference** *(chronological order)* | **Task(s)** | **Major finding(s)** |
|---|---|---|
| Wapner et al., 1956 (Exp. 1) | To move a luminant rectangle laterally until it appears straight-ahead under conditions of induced danger (standing at the edge of a table in darkness) | Right-shift of subjective straight ahead when precipice on the left, but no comparable shift to either side when dangerous stimulus to the right |
| Drake, 1987 | To turn one's body/head/eyes 90° laterally in order to judge the likeability of photographs | More positive evaluations of right-sided photographs for the 30 men, but not for the 30 women |
| Drake and Ulrich, 1992 (Exp. 2) | To bisect horizontal lines. To indicate one's personal optimism about future life events | More optimistic subjects show larger rightward bias |
| Schiff & Truchon, 1993 | To judge whether the facial expression of chimeric and neutral faces was more positive or negative. During the task, the experimenter contract unilateral hand muscles of the participant to explore the effect of the right vs left stimulation on emotional judgments | Judgments of chimeric faces (half sad, half happy) show a negative bias when the left face was negative. This bias is reduced by contractions of the right hand, whereas left hand contractions had no effect. |
| Bassel & Schiff, 2001 | To judge an emotionally neutral film after unlateral vibrotactile stimulation of one forearm | More positive judgments after right-sided stimulation, no affects after left-sided stimulation |
| Crawford et al., 2006 (Expts. 1 to 3) | To watch affectively evocative pictures (positive or negative valence) at variable vertical locations on a screen and to later recall the position of each picture, displayed again, but in the centre of the screen | Remembered locations along the left/right axis were not influenced by the affect manipulation (but see Table 9, for significant effects in the vertical dimension) |
| Root et. al, 2006 | To respond with the left or with the right hand to identify the emotions of target faces | Faster right-hand response for positive faces and left-hand response for negative faces |
| Drago, 2008 | To bisect horizontal lines and to judge the emotional evocation of paintings | People who display greater accuracy in the line bisection task (who can better allocate attention) are more influenced by the emotional messages of the paintings. This result indicates the dominant role of the right hemisphere (temporo-parietal regions) for both spatial attention and emotion |
| Foster et al., 2008 | To place pegs carrying verbal emotional labels on a large board | Positively labelled pegs placed to the left of negatively labelled pegs (for effects in the proximal/distal dimension see Table 8) |

In more recent times, the simple dichotomy “left hemispace – negative emotions” versus “right hemispace – positive emotions” has been revised (Demaree et al., 2005). It has been replaced by the “motivational-direction model” of emotional hemispheric processing (Harmon-Jones, 2004). This model suggests a LH / right hemispace dominance for approach-related emotions (including anger, a rather negative emotion; van Honk & Schutter, 2006) and a corresponding dominance of the RH for withdrawal-related emotions. This dimension, although most relevant to the lateral-horizontal axis, leads us to a discussion of the near space / far space distinction along the radial expansion of the space around us.

*Affect and attention along the radial axis (Tab. 8)*

In neuropsychology, a relevant distinction along the radial axis is the one between front space and back space (Viaud-Delmon et al., 2007). While the differences between these two spaces are evident, both phenomenally and from an action-perception point of view, there is a less elaborate distinction between two different compartments *within* front space. Attention in “near” and “far” space is differently coded by the brain; the clearest clinical evidence originating perhaps from the field of hemispatial neglect. This disorder can be double dissociated, i.e. there are patients showing neglect in near, but not far space (Halligan & Marshall, 1991), and other patients, whose signs of neglect are confined to far space (Vuilleumier et al., 1998). The functional neuroanatomy underlying this distinction is arguably a LH/near space and RH/far space processing specialization (Weiss et al., 2000). While these observations describe an interaction between processing deficits along the radial dimension and a variable relevant to the left/right dimension, i.e. a lesion typically in the RH, some work in healthy subjects suggests opposite hemispheric specialization for stimuli in near and far space. Specifically, it is assumed that the LH, because of its general motor dominance, directs attention preferably to near-peripersonal, grasping space, while the RH is more specialized for the analysis of stimuli in visual-extrapersonal, far space (Heilman et al., 1995; Graff-Radford et al., 2006; but see Bjoertomt et al., 2009 and Previc et al., 2005), for an alternative view. This near-space/LH and far-space/RH dichotomy is compatible with extended valence theories of emotional hemispheric processing, which postulate a LH dominance for approach (mostly positive emotions) and a RH dominance for flight or withdrawal responses, typically elicited by negative emotional stimuli. However, investigations of the interactions between emotional processing in near vs. far space (Tab. 8) do not usually make reference to functional hemispheric differences. Two research paradigms dominate. One uses a motor response away respectively towards the participant's body (Chen & Bargh, 1999; Markman & Dietrich, 2000). The findings are clear; there is a compatibility effect with faster responses for positive-emotional (negative-emotional) stimuli for the approach (avoidance) response mode. This compatibility is interpreted as reflecting a short-cut of the cognitive system to embodied meaning: negative stimuli are better kept at a distance, whereas what is positive and desirable is worth to be approached. However, closeness to one's body is only one factor involved; if the location of the response keys in relation to the stimulus is made especially salient, emotional-spatial compatibilities may be observed in a stimulus-centered frame of reference (Markman & Brendl, 2005; Seibt et al., 2008; see Tab.8).

Another paradigm requires subjects to respond to stimuli of differing affective valence with a flexion response (characteristic of making contact with an object) or with an extension response (rather activating an avoidance system). Stimuli, evaluated during maintenance of isometric arm extension or flexion are commonly judged later as more or less likeable (Cacioppo et al., 1993). Even the mere extension vs. flexion of one single finger to elicit the motor response can be effective to bias the advantage for positive or negative stimuli (Seibt et al., 2008; Tab. 8). To our knowledge, only one study has investigated interactions between flexion/extension movements and the approach/avoidance specialization of the two cerebral hemispheres. Maxwell & Davidson (2007) showed in a divided-visual field task with laterally exposed distally or proximally pointing arrows that the proximal bias for flexion and the distal bias for extension is asymmetrically organized across the two hemispheres (larger in the LH). Their experiment appears promising for future studies of spatial-emotional interactions in that it may help to reconcile hemispheric difference models with cognitive theories relying on an embodied meaning of approach and avoidance.

Other, more isolated research paradigms involve the estimation of the physical distance of positively or negatively valenced items (Balcetis & Dunning, 2010) or the priming of an emotionally evaluative response by presenting subjects with short or long physical distances (Williams & Bargh, 2008). Not readily compatible with the view of an action-based association between emotion and physical distance in the front plane are the results of Foster et al. (2008). These authors had subjects place pegs on an “emotional pegboard”. Pegs carried the labels of 6 basic emotions, and those positively labelled were placed farther away from one’s body (and, as discussed in the preceding paragraph, on the left side of the board). It is doubtful, however, whether a simple verbal label can induce a corresponding emotional state, and the authors proposed themselves that alternative measures of affect induction (e.g. the activation of emotional memories) should be tried out. Surprisingly, one methodology to reliably quantify spatial attention along a radial axis appears to be absent in the work on interactions between emotion and space. This is the simple task of radial line bisection that we have employed in the present study.

**Table 8: Synopsis of 10 experiments on interactions between healthy human subjects' emotional processing and attention along the radial axis**

| **Reference** *(chronological order)* | **Task(s)** | **Major finding(s)** |
|---|---|---|
| Cacioppo et al., 1993 (Exp. 1 and 2) | To rate the pleasantness of Chinese ideographs presented during either arm flexion or arm extension | Ideographs presented during flexion were rated more pleasant than ideographs presented under extension |
| Chen & Bargh, 1999, Exp. 1 | To pull or push a lever to categorize visually presented words as good or bad (group one: pull for good, push for bad, group two: opposite action/valence assignment) | Faster reaction times for pull responses to positively evaluated words and faster reaction times for push responses to negative words |
| Chen & Bargh, 1999, Exp. 2 | To pull or push a lever on detecting words visually presented at random time intervals. Words were positive or negative in meaning and response action (pulling, pushing) was blocked in a counterbalanced within-subjects design | Faster reaction times for pull responses to positively evaluated words and faster reaction times for push responses to negative words |
| Neumann & Strack, 2000 | To categorize highly emotional adjectives presented on a computer screen as positive or negative during continuous arm flexion or arm extension | Faster categorization of positive words during arm flexion and faster categorization of negative words during arm extension |
| Markman & Brendl, 2005 | To pull or push a lever to categorize positively or negatively valenced words presented on a computer screen, either distal or proximal to the subject's own name | For positively evaluated words faster responses towards the location of the self (one's first name), for negatively evaluated words faster away-from-self responses |
| Foster et al., 2008 | To place pegs carrying verbal emotional labels on a large board | Positively labelled pegs placed distally of negatively labelled pegs (for effects in the lateral-horizontal dimension see Table 7) |
| Seibt et al., 2008 | To use two response keys (or a joystick) to classify emotionally negative or positive words or pictures of old or young people. Keys (joystick position) close or distant to the stimulus | Reaction time advantage for positive stimuli on the key closer to the stimulus. Body/self-centered vs. object-centered reference frames can be altered by instruction |
| Williams & Bargh, 2008 (Studies 1 to 4) | To judge the pleasantness of an embarrassing story, one's mood after a violent story, to estimate the number of calories in unhealthy food and to rate the strength of bonds to family and friends after being primed with small or large physical distances | Compared to priming with spatial closeness, priming with spatial distance leads to lessened emotional impact of negative stimuli and to decreased emotional attachment to family and friends |
| Balcetis & Dunning, 2010 (Studies 1 to 3) | To rate the physical distance of physiologically or socially desirable objects; to throw a ball towards objects of varying emotional significance | Shorter estimated distance for emotionally more attractive items, both by numerical ratings and ball throwing |
| Drago et al., 2010 | To freely set a mark on an empty sheet of paper after the evocation of positive or negative emotional memories | Positive emotional memories induce a distal bias and sad memories induce a proximal bias |

*Affect and attention along the vertical extension (Tab. 9)*

On first consideration, the association between positive emotions and upper space and that between negative emotions and lower space, although crossculturally surprisingly invariant (Yu, 1995), seems to be entirely symbolic. However, upper and lower visual fields are characterized by different functional specializations in the primate visual system (Previc, 1990), and various higher-order cognitive operations are reportedly drawing on these differences (Goldstein, 2001; Niebauer & Christman, 1998; Previc et al., 2005; Previc & Intraub, 1997). Even abstract concepts such as religiosity incorporate dissociations in the meaning of up and down that may ultimately be grounded in basic properties of perception and action (Meier et al., 2007; Previc et al., 2005). Table 9 lists 9 experiments on the interaction between emotional and spatial processing along the up-down axis. The paradigms used range from projecting one's subjective horizon (Wapner et al., 1957; Fisher, 1964) to the evaluation or inspection of emotional stimuli exposed in the upper or lower half of the visual field (Crawford et al., 2006) and to forced body positions (upright vs. slumped; Wilson & Peper, 2004) during the evocation of emotional thoughts. Uniformely, there was a processing advantage for positively (negatively) valenced stimuli in the upper (lower) parts of the visual field, or the processing of upper (lower) visual field stimuli biased later emotional judgments towards the positive (negative) side. When participants' spatial biases were measured as a function of their emotional state, either as a trait variable or experimentally manipulated, positive relative to negative emotions invariably induced upward shifts in spatial attention (Fisher, 1964; Wapner et al., 1957). Recently, Casasanto and Dijkstra (2010) had participants move marbles either from a lower to a higher level or in the reverse direction. Movement direction influenced the retrieval time for autobiographic memories (negative or positive, by instruction). Specifically, positively valenced memories were retrieved faster during upward movements, and the retrieval of negatives memories was speeded up by downward movements. The only investigation requiring subjects to draw lines to represent the emotional content of a list of words (Lundholm, 1921) found upward slopes for positively and downward slopes for negative affect. To our knowledge, vertical line bisection, despite its use in normal subjects (Jeerakathil & Kirk, 1994), has not been used in studies on spatial-emotional interactions.

**Table 9: Synopsis of 9 experiments on interactions between healthy human subjects' emotional processing and attention along the vertical axis**

| **Reference** *(chronological order)* | **Task(s)** | **Major finding(s)** |
|---|---|---|
| Lundholm, 1921 | To represent the affective tone of adjectives by drawing lines (no further instructions as to line orientation) | The majority of negatively (positively) toned words were represented by lines with a downward (upward) directional tendency |
| Wapner et al., 1957 | To adjust the vertical extension of one's straight-ahead ("subjective horizon") after getting (veridical) information of having passed or failed a mid-term examination | Compared to a neutral baseline, A marks produced upward-shifts and F marks downward-shifts in the subjective horizon |
| Fisher, 1964 | To describe the movement direction in an illusory motion paradigm and to adjust the vertical extension of one's straight-ahead ("subjective horizon"). To give a verbal description of (neutral) emotional facial expressions | Subjects, who used more sadness-related adjectives in the description of facial expressions (1) perceived more downward illusory motion trajectories and (2) showed stronger downward-shifts in the subjective horizon |
| Meier & Robinson, 2004 (Study 1) | To evaluate positive and negative emotional words presented in the upper or lower half of a computer screen | Positive words were faster evaluated when presented in the upper half, negative words when presented in the lower half |
| Meier & Robinson, 2004 (Study 2) | To evaluate emotional words in the centre of a computer screen prior to perform a letter discrimination task with stimuli in the upper or lower half of the screen | Positive evaluations primed letter discriminations in the upper field, negative evaluations primed discriminations in the lower field |
| Wilson & Peper, 2004 | To generate positive or negative thoughts while in an upright or slumped body posture and to rate task difficulty separately for the two posture conditions | The majority of participants indicated that the generation of specifically positive thoughts was easiest in the upright posture |
| Crawford et al., 2006 (Exp. 1 to 3) | To watch affectively evocative pictures (positive or negative valence) at variable vertical locations on a screen and to later recall the position of each picture, displayed again, but in the centre of the screen | Relative to negatively valenced pictures, positively valenced pictures were biased towards upward locations in memory |
| Casasanto and Dijkstra, 2010 (Exp. 1) | To retrieve positive or negative autobiographical memories while moving marbles either upward or downward (Instruction e.g. "*tell me about a time you felt proud of yourself*") | Positive memories retrieved faster during upward movements, negative memories during downward movements |
| Casasanto and Dijkstra, 2010 (Exp.2) | Same apparatus as in Exp. 1, but with valence-neutral instruction (e.g. "*tell me about an event that happened yesterday*") | Direction of movements determines emotional content of memories. Moving marbles upward caused participants to retrieve more positive memories, moving them downward more negative memories |

In the present study we set out to compare the impact of positive and negative emotions on line bisection, both in the horizontal and radial extension. We used the contemplation of autobiographic memories as a potentially biasing trigger and predicted a leftward and distal bias during the evocation of negative memories and a rightward and proximal bias for positive emotions. By testing also a group of children, we wanted to explore whether the emotion-space interactions would resemble those found in the adult participants. Because of constraints in the time available for testing the children, we renounced including line bisection in the vertical dimension.

*Methods*

*Participants*

The experiment was performed in accordance with the ethical guidelines of the Declaration of Helsinki, and adult subjects provided written informed consent before participating. Forty healthy undergraduate men of the University of Zurich participated in the experiment (mean age = 22.7 years, SD = 2.2 years). All subjects were right-handed according to a 13-item handedness inventory (Chapman & Chapman, 1987). An uneventful history of neurological or psychiatric diseases and of any substance abuse and learning disorders was assured by means of a brief neuropsychiatric interview (Campbell, 2000). In addition, we tested 35 children (20 girls) age six or seven, all right-handed according to the hand spontaneously used in the bisection tasks. They were recruited from the primary school of Bellinzona (Switzerland). According to teacher information and inferred by the absence of any medication use, none suffered from any neurological or psychiatric disease.

*Tasks and Procedure*

Participants were required to mark, with a sharp pencil held in the dominant right hand, the midpoint of each of 48 lines. There were two conditions, one inducing a positive emotional state, the other a negative emotional state. In each condition, 12 horizontal lines and 12 radial lines, all 26.0 cm long, had to be bisected. Horizontal and radial lines were presented blocked, but one line after the other on A4 sheets positioned in the participant's midsaggittal plane. Order of line orientation and emotion condition was counterbalanced across subjects.

Adults were individually tested, children in two groups of 17 subjects each. Before starting the bisection task, adults were instructed to remember a highly emotional personal life event (negative or positive) and to contemplate this event as vividly as possible during the entire condition. Each sheet was removed by the experimenter as soon as a bisection was performed (there was an interval of about 3 seconds between trials). Children were analogously instructed, but had to imagine "something very pleasant" or "something very unpleasant", and examples were provided for pleasant (eating ice cream, making a ride on a favorite city) and unpleasant events (having seriously hurt oneself, being punished for having committed something forbidden). Once having bisected a line, each child turned the page. Deviations from the objective midpoint were measured to the nearest 0.5 mm (negative values indicating leftward and proximal bias), and means for the two types of line orientation and emotion condition were calculated separately.

**Table 10: Experimental design of study 3**

| | **Variables** | **Levels** | **Operationalization** |
|---|---|---|---|
| **Independent variables** | Type of induced emotion<br><br>Axis<br><br>Age Group | Positive<br>Negative<br><br>Horizontal<br>Radial<br><br>Adults<br>Children | |
| **Dependent variables** | Average deviation from mid-line | | Calculation of the average displacement from mid-line in mm over all 12 lines for each participant |

*Results*

<u>*Horizontal Line Bisection*</u>

Fig. 7 displays the mean deviations in horizontal line bisection for adults and children and the two emotion conditions separately. A repeated measures ANOVA of the average deviation (Grand mean = -2.98 mm, SD = 5.08 mm) with emotion condition (positive, negative) as within-subject factor and age group as between-subject factor revealed two main effects: (1) a main effect of age group ($F(1,73) = 11.1$, $p < .001$); overall leftward displacement was larger in children compared to adults. (2) A main effect of emotion condition ($F(1,73) = 6.4$, $p < .01$) indicated that leftward displacement was larger after negative compared to positive emotion evocation. The interaction was clearly not significant ($F(1,73) = .40$, $p > .5$).

One sample t-tests of the overall bias (mean of all bisections, collapsed over both emotion conditions) indicated a marginally significant leftward deviation for adults (mean = -1.26 mm, SD = 3.83 mm; $t(1,39) = 2.08$, $p = .044$) and a highly significant leftward deviation for children (mean = -4.94 mm, SD = 5.66 mm; $t(1,34) = 5.16$, $p < 0.001$). See Fig. 7 for illustration.

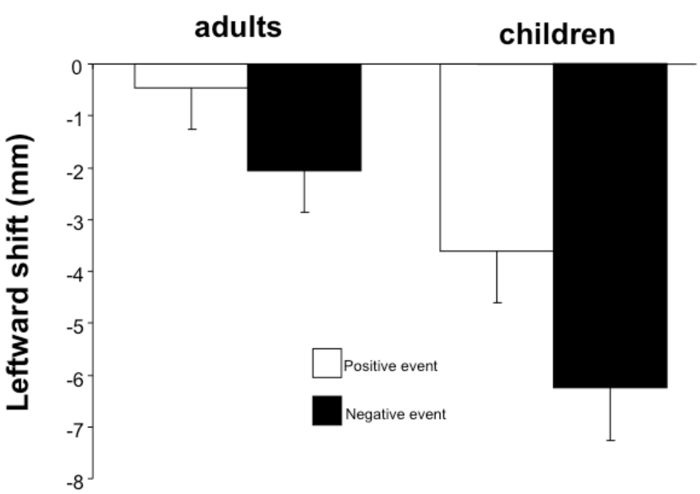


**Figure 7: Magnitude of pseudoneglect (left-sided attentional shift) under contemplation of a positive event (white bars) and a negative event (dark bars) for adults (n= 40) and children (n= 35).** Error bars represent standard errors of the mean.

Both groups displayed a significant leftward deviation under contemplation of negative events (Children group: paired t-test, t=6.73, p=<.0001; Adults: t=2.37, p=.022). Within the *children group*, the magnitude of leftward shift was significantly different between conditions (t=2.77, p<.01, two-tailed; analogous values for adults: t=1.20, p=.23).

A repeated measures ANOVA of the average deviation only within the *children group* revealed no significant main effect of gender (F(1,33)=.130, p=.721) nor any interaction involving the factor gender (F(1,33)=1.877, p=.180).

A repeated measures ANOVA of the number of bisections with emotion (positive, negative) and direction of bias (leftward, rightward) as within-subject factors and age group as a between-subject factor revealed a main effect of direction of bias (F(1, 73) =14.57, p<.001), but no main effect of emotion (F(1,73)=.118, p= .732). There was also a main effect of age group (F(1,73)= 314.30, p<.001); children were less accurate than adults, regardless of the direction of the deviation. Among the two-way interactions only the interaction between emotion and direction of shift was significant (F(1,73)=6.878, p=.011). Contemplating negative events resulted in a higher number of leftward shifts. The triple interaction was also not significant (F(1,73)=.095, p= .758).

A repeated measures ANOVA of the number of leftward vs rightward bias only within the *children group* revealed no significant main effect of gender (F(1,33)=2.635, p=.114) nor any significant interaction involving the factor gender.

*Radial Line Bisection*

A repeated measures ANOVA of the average deviation (grand mean = 8.12 mm, SD= 5.62 mm) with emotion condition (positive, negative) as within-subject factor and age group as between-subject factor revealed no main effects and no interaction (main effect of emotion: F(1,73) = 1.73, p > .19, main effect of age group: F(1,73) = 1.27, p > .26, interaction: F(1,73) = .14, p > .7). One sample t-test of the overall bias (mean of all bisections, collapsed over emotion conditions) revealed a significant distal bias in both adults (mean = 8.80 mm, SD = 4.12 mm; $t(1,39) = 13.5$, $p < .001$) and children (mean = 7.33 mm, SD = 6.94 mm; $t(1,34) = 6.25$, $p < .001$). A repeated measures ANOVA of the average deviation only with *children group* revealed no significant main effect of gender ($F(1,33)=.265$, $p=.610$) nor an interaction involving the factor gender ($F(1,33)=.041$, $p=.841$).

Repeated measures ANOVA of the number of far vs near bisections with emotion (positive, negative) and direction of bias (near, far) as within-subject factor and age group as between-subject factor revealed a main effect of emotion ($F(1,73)=309.01$, $p=.000$), but no main effect of direction of bias ($F(1,73)=.029$, $p=.614$. Among the two-way interactions only the interaction between emotion and age group was significant ($F(1,73)=64.68$, $p=.000$). The triple interaction was not significant ($F(1,73)=.013$, $p=.909$). A highly significant effect of age group was found ($F(1,73)=1179.543$, $p=.000$).

A repeated measures ANOVA of the number of far vs near bisections only within the *children group* revealed no significant main effect of gender ($F(1,33)=.070$, $p=.793$.) nor a significant interaction involving the factor gender.

*Discussion*

To investigate and quantify asymmetries in spatial attention a number of paper-pencil tasks exist. The line bisection task requires participants to spontaneously indicate the middle of horizontal lines of various lengths, presented on paper sheets. This task is traditionally used with neglect patients (Bisiach et al., 1983), where unilateral brain lesions (usually in the RH) induce an attentional shift away from the contralateral hemispace, bringing the most spectacular example of asymmetrical exploration of space (Kerkhoff, 2001). Even if in a less pronounced manner, biased space perception has been evidenced also in healthy subjects, in both left/right and near/far space. In fact, when bisecting horizontal lines, people tend to show a leftward bias, so-called "pseudoneglect" (Bowers & Heilman, 1980). When bisecting radial lines they erroneously displace the midline distal to the line's center (Chewning et al., 1998).

We know that attentional shifts in space are modulated by a number of factors, among which are gender, handedness, hand used for the bisection as well as age (Jewell & McCourt, 2000).

In the present experiment, we used the line bisection task, to our knowledge for the first time, to quantify the magnitude of horizontal and radial attentional shifts induced by temporary emotional states, in both children and adults.

It is plausible to suppose that, if metaphorical cognition mediates the emotion/space relation, children could be expected to show smaller effects, because of shorter exposure to common metaphors. On the other hand, some studies suggest the presence of synaesthetic cross-modality correspondences already in preverbal infants, so it cannot be excluded that also emotion/ space interactions do not need to be learned, but are already present at birth (Walker et al., 2010). Further evidence for the view that the interconnections between emotion and space are deeply rooted in an organism's nervous system, derives from studies on animals lateral biases in response to highly emotive stimuli.

*Horizontal line bisection*

Over both age groups and emotion conditions, our participants showed a significant leftward bias, i.e. pseudoneglect, well-known from studies on horizontal bisection (Bowers & Heilman, 1980). This pseudoneglect was marginally significant for adults, but highly significant for the children. This finding is in line with the results of previous investigations of age-related effects on bisection performance: with increasing age people tend to show a decreased leftward error (Fujii et al., 1995). Many studies indicate that pseudoneglect is stronger in younger than older and that young children show a generally low bisection accuracy (Jewell & McCourt, 2000; van Vugt et al., 2000).

Concerning the effect of emotion on direction of bisection error, we found a larger leftward displacement after negative compared to positive emotion evocation. This is in line with classical valence theories of emotional hemispheric processing, which propose a specialization of the LH for positive emotions and of the RH for negative emotions (Demaree et al., 2005).

However, although negative thoughts enhance pseudoneglect in both children and adults, this tendency is statistically significant only in children. One possible interpretation is that emotion exerts a decreasing effect on space exploration with an individual's increasing age. Alternatively, this effect could merely be an artefact of the overall larger bisection error in our children group. In fact, when looking at the difference between the two valence conditions as a percentage of the overall deviation, a different picture emerges. That is why this second explanation seems to be more convincing to us. We note that future research should include a baseline condition without any emotion evocation: this would probably help to clarify the actual impact of age on emotion-dependent attentional shifts.

The absence of a corresponding rightward shift induced by positive emotions could be related to the marked and robust tendency to always bisect to the left. Alternatively, negative emotional stimuli may be more powerful in modulating attention in space than positive stimuli (Crawford & Cacioppo, 2002; Pourtois et al., 2006; Pourtois & Vuilleumier, 2006).

*Radial line bisection*

Looking at the bisection mean of all radially placed lines collapsed over emotional valence, we found a significant distal bias in both adults and children, which supports results from previous studies (Barrett et al., 2002). Contrary to our hypothesis that positive affects will trigger approach behavior ("near space" bias), whereas negative affects rather leads to avoidance behavior ("far space" bias), remembering or imagining emotional events did not influence attention along the near/ far space axis. This null finding appears puzzling in view of the many studies that described an emotional mediation of proximal-distal gradients in spatial attention (see Table 8). Our failure to establish an association may indicate that line bisection is less suitable to monitor emotion/space interaction along the radial (compared to the horizontal) axis. As evident from a comparison of Table 7 and 8, the emotional connotations of "left" and "right" are arguably more direct and less metaphorical than those of "near" and "far".

The line bisection task chosen for this study has the advantage to be brief and easy to administer, also with children. However, a disadvantage is that many factors may modulate performance. In order to optimally reduce the influence of factors other than emotion, follow-up studies should carefully control hand and eye movements during the act of bisection. More generally, the focus should be put on the development of alternative methodologies, able to differentiate the influence of a temporal emotional state on the passive perception of space from that on the active exploration of space. Presumably they will also help to elucidate the nature of near/ far asymmetries related to emotion. Finally, future studies should consider both participant's emotional state and traits, as their interactive effects on spatial processing is largely unknown.

*Conclusion*

In our study, emotions influenced the magnitude of attentional shifts on a left/right axis, but not on a near/ far dimension. Remembering or imagining negative events enhanced pseudoneglect, which suggest that an induced temporary emotional state is able to bias the way we perceive and explore space. If anything, the effect of emotion on spatial attention seems to be larger for children than for adults.

From a most general point of view, our findings of a tight interconnection between emotional and spatial processing add to a growing literature indicating the parietal lobes as key structures for the processing of non-physical aspects of space. Relational reasoning (Hinton et al., 2010), social distance (Yamakawa et al., 2009) and empathic concern (Thakkar et al., 2009) have all been discussed in the frame of parietal contributions to symbolic space. It is well possible that emotion may turn out to be a crucial mediator of these contributions

# 3
# Discussion

Self-awareness refers to the conscious experience of our own individuality. This term describes the ability to perceive, appreciate and evaluate one's own existence, including one's own traits, feelings and behaviors. It undoubtedly represents a fundamental aspect of our life, giving significance to our human experience in the world. After all, what value would our existence have if we would not have the opportunity to be aware of it?

There are many kinds of self-awareness. Among the most important is the capacity to attribute one’s own thoughts, emotions and body movements to one’s self and to make a subjective experience of them. Self-awareness includes the experience of existing in time, as an individual, with a past and a future, in a network of social relationships. It enables us to consciously experience the temporary intentions and goals, which guide our actions.

The conscious experience of being an *individuum* separated from others results from a construction, performed continuously by our brain, in relation with external and interoceptive changes. The self is highly malleable and subject to a laborious process of shaping: in fact, activity in the brain creates an experience of the outside world and an “internal image” of our individuality. The cerebral hemispheres perpetually integrate and process the multisensory information coming from the outside world, combining it with the internal emotional and cognitive changes. Through this process, they continuously revise and update the subjective self-experience.

Studies of brain damage evidenced that in some cases, our brain fails to construct a truthful image of the self, and it creates false knowledge. Abnormal neural activity may result in a false knowledge of the physical world. Auditory, visual or tactile hallucinations are typical manifestations of the fallibility of our brain and of the inherent fragility characterizing "reality".

Sometimes, alterations in functional circuits result in an altered experience of one's own individuality, like in the case of autoscopic phenomena (i.e. reduplications of one's own body and perceived self; Brugger et al., 1997), of phantom limbs (Melzack, 1992) , or of confabulatory behaviors (Mckay & Kinsbourne, 2010).

Awareness of illness is one of the facets of self-awareness. As other kinds of awareness, the appreciation of one's health state is characterized by an essential subjectivity (Metzinger, 2002).

Patients suffering from anosognosia lack the ability to recognize a specific illness or deficit: during some hours or days, they are themselves free from the obviousness given by their senses. Their own brain tells them that they are healthy, able to move, to see, or to speak just like every other normal person. Since a failure in illness recognition has serious consequences for recovery and may impair the efficacy of rehabilitative measures, the study of this disorder is not only of theoretical interest, but also of great clinical relevance.

Anosognosia involves unawareness of a specific impairment. The lack of awareness can take many forms: hemiplegic patients may fail to acknowledge their motor impairment; blind persons may claim that they can see; aphasics may be completely unaware of their language deficits. Similarly, Alzheimer's patients may fail to acknowledge their memory impairment and patients suffering from hemispatial neglect may seem convinced of equally exploring both sides of space.

In all forms of anosognosia, unawareness can vary in severity, reaching from a simple indifference toward one's own illness or deficit to an active and vehement denial of one's own disability accompanied by confabulation. Anosognosic symptoms may fluctuate and in case of AHP they usually become less intense over time. They occur more frequently and are more severe after RH lesions, and their incidence is higher after large lesions, comprising a wide range of cortical and subcortical brain areas. In the last two decades, many authors investigated the anatomical correlate of denial trying to identify which regions are specifically damaged when anosognosia is observed. While most studies agree that lesions usually involve the RH, the intra-hemispheric localization of the damage leading to anosognosia appears more controversial.

Clinical evidence suggests that the ability to detect illness or impairment may be, as many other cognitive functions, lateralized. Many behavioral and lesion studies provided evidence that a functional balance between the two cerebral hemispheres is required to assure an emotional equilibrium (Davidson & Sutton, 1995; Gainotti, 1972). In the same way, a functional balance seems to be necessary for a correct detection of one's own dysfunction (Ramachandran, 1995).

A century of research led to the conclusion that denial of illness does not result simply from the need to protect oneself from sadness or depression, nor is there evidence that it would constitute a sign of global intellectual impairment (Marcel et al. , 2004; Orfei et al. , 2007).

However, current theories of anosognosia suffer from a lack of specificity and fail to characterize a common neural mechanism, which is impaired in different forms of unawareness of illness. For instance, recent explanatory models of AHP mainly focus on the role of altered intentionality and motor mechanisms' disruption, which are nowadays considered to be responsible for generating unawareness of motor failure (Frith et al., 2000; Berti et al., 2005; Fotopoulou et al., 2008). Nevertheless, these explanations are suitable only for AHP. Present-day models are not able to explain the marked incidence of RH lesions among patients with the disorder. They also fail to account for different forms of anosognosia.

The primary purpose of this thesis was to draw attention to the cognitive processes accountable for different forms of anosognosia. We wanted to provide a satisfactory explanation of the higher incidence of RH damages that distinguishes the clinical heterogeneity of the phenomenon (Breier et al., 1995; Pia et al., 2004).
In attempting to identify the neural network essential for the appraisal of one's own well-being we focused on the study of healthy positive illusions. We introduced the term of *nosognosia*, the normal function that is impaired in anosognosia. Nosognosia refers to a capacity for evaluating our current level of physical and mental well-being and detecting dysfunction. We have put *anosognosia* and *nosognosia* on a continuum and demonstrated that the same mechanism involved in the obstinate denial of illness is probably implicated in the illusion of invulnerability that characterizes healthy nosognosia.

We discovered that the activation of the *right* parieto-insular cortex, but not of the *left* - realized using cold water irrigation of the left external ear – reduces unrealistic optimism for one's own future health state in a way comparable to the temporary abolishment of anosognosic denial. The observed effect, resulting from a physiological manipulation of unilateral brain activity, corroborates a neural basis of positive illusions (Sharot et al., 2007). Most important, besides opening new ways in the field of anosognosia research and on the possible intertwining between pathology and normality, this finding highlights the asymmetrical contribution of the cerebral hemispheres to illness awareness (Ramachandran, 1994, 1995).
The majority of authors agree that the contribution of the right hemisphere to an individual's self-awareness is larger than that of the left hemisphere (Devinski, 2000). Our results on healthy individuals support this view, suggesting that the function we called *nosognosia* is most likely based on a delicate functional balance between the two hemispheres. Recent neuroimaging studies indicated the insular cortex as a relevant anatomical region, crucially involved in different aspects of self-awareness (Karnath et al., 2005; Craig, 2009). More specifically, we think that the *right* parieto-insular cortex is a key structure essential for the appraisal of one's own physical and cognitive functionality. Presumably, the disruption of neural network involving this

structure through structural, functional or effective connectivity (Friston et al., 1993b) may be responsible for different forms of anosognosia.

The secondary aim of this thesis was to investigate functional hemispheric asymmetries that lead to subjective emotional experience. In particular, we focused on the interplay between emotional processing and spatial attention. Studies from both human and animal research evidenced a specialization of each hemisphere for dealing with information incoming from the contralateral hemispace, which coincides with a similar specialization for stimuli that have a positive or a negative valence. Many authors found a superiority of the right hemisphere in detecting threatening information and reported an association between negative affect and left hemispace (MacNeilage et al., 2009; Demaree et al., 2005; Kinsbourne, 1978). In study 1 and 2, we tested the validity of this theory in a sample of healthy participants. We found that the presence of attentional asymmetries on a left/right axis – quantified using the line bisection task – predicted the reaction times for the recognition of verbal stimuli with emotional valence. Participants displaying a leftward line bisection bias, recognized negative words more quickly. Subsequently, we discovered that temporary emotional states influenced the way we explore space. Remembering or imagining negative events enhanced leftward shift in spatial attention. These results corroborate the different contribution of the cerebral hemispheres in the modulation of our emotional experiences and the predominant RH role in negative emotional processing. They confirm the influence of the parietal lobes in the processing of non-spatial information (Yamakawa et al., 2009; Thakkar et al., 2009) and the strong relationship linking spatial attention and emotional experience (Drago et al., 2008).

The present doctoral thesis has thus produced to two major findings.
First, we found evidence for a common neural basis of healthy unrealistic optimism and pathological anosognosia. This supports the view that no clear division separates pathological from healthy states. We know that normal self-awareness is dependent on several parallel processes. Although it is likely that independent neural

mechanisms are responsible for different forms of anosognosia, we strongly propagate the existence of a single high-level cognitive process, a "nosognosia system" decisively responsible for the detection of dysfunction, to whom impairment is accountable for both healthy positive illusions related to illness and anosognosic confabulatory behaviors. The functionality of this system relies on an interhemispheric balance (Ramachandran, 1994, 1995).

Future researchers should, in our opinion, look for new ways to study functionality and lateralization of the nosognosia system.

They should more explicitly inquire about the effect of right parieto-insular damages on positive bias related to one's own illness, applying alternative experimental methods (for instance TMS), able to modulate small brain regions in a more selective manner. The CVS method is safe, inexpensive and non-invasive; however it presents some limits. In fact, it influences brain activity in different areas and some argue that its effect lacks specificity. We think that new promising techniques for modulating brain activity, as for example the combination of TMS and high-density EEG (Massimini et al., 2005), should be exploited to explore how changes in effective connectivity linked to right parietal damages influence awareness of illness.

Finally, experimental research should further investigate the impact of individual differences in baseline hemispheric activity in frontal and parietal brain regions on the capacity to detect and process threatening self-related informations.

Second, our results corroborate a superiority of the right hemisphere in processing negative self-related information. We argue that the parietal contribution for non-physical aspects of space needs further examination. This is a critical aspect, especially to the aim of deepening the understanding of neurological disorders, resulting from damages to this region. In particular, studies on anosognosia should broaden the spotlight of attention toward the role of right parieto-insular areas in mediating negative affects related to illness detection.

The appraisal of one's own well-being is inseparable from one's own internal feeling states and emotion-related cognitions. For this reason, a more systematic study of possible interactions between emotional imbalance and the inability to detect illness may lead, in our opinion, to a deeper understanding of the neural system implicated in anosognosic denial.

Finally, follow-up studies should aim to elucidate how emotions modulate parietal space processing. Particular consideration should be given to the modulation of perception and exploration of space by emotional states and traits.

# 4
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# 5. Curriculum vitae

## Corinne Tamagni

| | |
|---|---|
| Date of Birth | September 4, 1982 |
| Place of Birth | Locarno, Switzerland |
| Citizenship | Swiss |

**Education**

| | |
|---|---|
| 03/2011 | PhD in Psychology, University of Zurich<br>International PhD Program in Neuroscience,<br>Neuroscience Centre Zurich, ZNZ |
| 10/2006 | Master of Science in Psychology, University of Lausanne |
| 06/2001 | High School Degree, Liceo Bellinzona |

**Employments**

| | |
|---|---|
| 03/2008 - 04/2011 | Neuropsychological Unit, Neurology, University Hospital Zurich (USZ)<br>*PhD Student and clinical assistant* |
| 10/2007 – 02/2008 | Kantonale Psychiatrische Dienste (KPD), Liestal (Basel)<br>*Research Internship* |
| 07/2007 – 09/2007 | Neuropsychological Unit, Dept. of Neurology, University Hospital Zurich (USZ)<br>*Research Internship* |
| 03/2007 – 06/2007 | Geriatric Unit, Hospital Beata Vergine, Mendrisio<br>*Clinical Internship* |

**List of publications**

McKay, R., Tamagni, C., Palla, A., Brugger, P. *Unrealistic optimism in healthy subjects: "Prospective anosognosia"?* Submitted to The Neuroscientist.

Tamagni, C., Palla, A., Krummenacher, P., Vitacco, D., Huberle, E., Straumann, D., Hegemann, S., McKay, R., Brugger, P. (2010) *Vestibular stimulation reduces unrealistic optimism.* Nature Precedings

Tamagni, C., Mensen, A., Brugger, P. *Anticipatory awareness in healthy individuals: exploring unrealistic optimism.* In preparation.

Tamagni, C., Croce, S., Brugger, P. *Contemplating negative events induces leftward deviation in line bisection.* Submitted to CABN.

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**Poster presentations**

Hilti, L.M., Tamagni, C., Palla, A., Brugger, P. (2010) *Amputation desire: no alleviation by caloric vestibular stimulation*. Annual Meeting Society for Neuroscience, San Diego.

Tamagni, C., Vitacco, D., Palla, A., Hotz, P., Krummenacher, P., Huberle, E., Straumann, D., McKay, R., Brugger, P. (2010) *Vestibular stimulation reduces unrealistic optimism.* Twenty-eight European Workshop on Cognitive Neuropsychology, Bressanone.

Baumann, H., Loetscher, T., Tamagni, C., Brugger, P. (2009) *Spacetime: neglect of early relative to late events after right hemisphere damage.* Jahrestagung der Schweizerischen Neurologischen Gesellschaft SNG, Interlaken.

Tamagni, C., Lotscher, T., Brugger, P. (2009) *Standing on a clockface: a mind's eye exploration of backspace*. Zentrum für Neurowissenschaften Zürich (ZNZ) Symposium, ETH Hönggerberg, Zürich.

Tamagni, C., Mensen, A., Croce, S., Wettstein, V., Brugger, P. (2009) *Remembering negative events induces lefward deviation in a line bisection task*. 3rd Annual meeting of the Social & Affective Neuroscience Society, New York.